The University of Birmingham

PHARMACEUTICAL INDUSTRY PERSPECTIVES ON FACTORS THAT INFLUENCE THE ADOPTION AND DIFFUSION OF DRUGS IN THE UK: FOUR CASE STUDIES

by

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ABSTRACT

Aim: To gather, analyse and present the views of personnel currently working within pharmaceutical companies relating to factors influencing drug diffusion (market penetration), using case studies to determine how their perspective relates to diffusion curves and literature-based timelines describing the same phenomenon.

Methods: Qualitative study based on semi-structured interviews with marketing, market access or senior management personnel from eight major UK R&D pharmaceutical companies. Case studies were selected through expert consultation. Diffusion curves were produced for all potential case study drugs (n=21) and timelines constructed from the literature and augmented with clinical expert input.

Results: Thematic analysis of 15 interviews conducted across four case studies: bisphosphonates; atypical antipsychotics; phosphodiesterase type 5 inhibitors and statins revealed 10 diffusion themes: clinical need; clinician/patient experience; clinical evidence; health service/policy environments; adopter attitude; communicating relative advantage; market development; opinion leaders; company cultural heritage/perception and pricing. Triangulation with diffusion curves and literature-based timelines demonstrated a high level of convergence between accounts. Points of divergence revealed unique pharmaceutical industry insights.

Conclusion: Eliciting diffusion knowledge from this under-researched stakeholder group largely confirmed issues previously outlined in the literature, but importantly has revealed the significance of less tangible social interactions that inform perceptions of new pharmaceuticals that can significantly influence adoption and diffusion.

For Mom

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ABBREVIATIONS

AA/s	Atypical antipsychotic/s (second generation)
ABPI	Association of the British Pharmaceutical Industry
AHSNs	Academic Health Science Networks
ACE-inhibitor	Angiotensin-converting enzyme inhibitor
ARR	Absolute risk reduction
AUA	American Urological Association
AUC	Area under the curve
Av	Average
BASHH	British Association of Sexual Health and HIV
BMA	British Medical Association
BMD	Bone mineral density
BMJ	British Medical Journal
BMS	Bristol-Myers Squibb
BNF	British National Formulary
BP/s	Bisphosphonate/s
BSSM	British Society for Sexual Medicine
CA/s	Conventional antipsychotic/s (first generation)
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCTs	Controlled clinical trials
CEO	Chief Executive Officer
cGMP	Cyclic guanosine monophosphate
CHD	Coronary heart disease
CSM	Committee for the Safety of Medicines
CV	Cardiovascular
CVD	Cardiovascular disease
DA	Disease awareness
DDD	Daily defined dose
DEXA	Dual-energy X-ray absorptiometry
DH	Department of Health
DTB	Drugs and Therapeutic Bulletin
EAU	European Association of Urology
EC	European Community
ED	Erectile dysfunction
EDA	Erectile Dysfunction Association
EmBASE	Embase excerpta medica database
EMA	European Medicines Agency (formerly EMEA)
EMEA	European Agency for the Evaluation of Medicinal Products (became the EMA in December 2009)
EPS	Extrapyramidal symptoms
EU	European Union
FDA	Food and Drug Administration
FLS	Fracture Liaison Service
GAQ	Global assessment question

GI	Gastrointestinal
GMC	General Medical Council
GMS	General Medical Services (contract)
GP/s	General practitioner/s
GSK	GlaxoSmithKline
h	hours
HCHC	House of Commons Health Committee
HDL-C	High-density lipoprotein cholesterol (‘good’ cholesterol)
HIRU	Health Impact Research Unit
HMG-CoA	Hydroxmethylglutaryl CoA (reductase inhibitors i.e. statins)
HPLD	Hyperlipidaemia
HRT	Hormone replacement therapy
HSC	Health Service Circular
ICD	International Classification of Diseases
IIEF	International Index of Erectile Function questionnaire
IM	Intramuscular
IOF	International Osteoporosis Foundation
IU	International units
JBS	Joint British Society
JES	Joint European Society
KOLs	Key opinion leaders
LDL-C	Low-density lipoprotein cholesterol (‘bad’ cholesterol)
MALES	Men’s Attitudes to Life Events and Sexuality
MCO	Managed Care Organisation
MD	Mean difference
mg	Milligram
mg/dL	Milligrams per decilitre (1mmol = 0.026mg/dL)
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial infarction
mins	Minutes
mls	Millilitres
mmol/L	Millimoles per litre
MS	Multiple sclerosis
MSD	Merck Sharp & Dohme
NAION	Non-arteritic anterior ischaemic optic neuropathy
NCEP	National Cholesterol Education Program (USA)
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIH	National Institutes of Health
NIHR HSC	National Institute for Health Research Horizon Scanning Centre
NIHR CRN	National Institute for Health Research Clinical Research Network
NIMH	National Institute of Mental Health
NO	Nitric oxide
NPC	National Prescribing Centre
ns	Non-significant
NSF	National Service Framework
NSF-CHD	National Service Framework for Coronary Heart Disease
OTC	Over the counter

P&G	Procter & Gamble
PAH	Pulmonary arterial hypertension
PANSS	Positive and Negative Syndrome Scale
PCOs	Primary Care Organisations (later became PCTs)
PCTs	Primary Care Trusts
PDE5	Phosphodiesterase type 5
PE	Pharmacoeconomic
PICTF	Pharmaceutical Industry Competitiveness Task Force
PMO	Postmenopausal osteoporosis
PPRS	Pharmaceutical Price Regulation Scheme
PSRs	Pharmaceutical sales representatives
Pt/s	Patient/s
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality adjusted life year
QOF	Quality and Outcomes Framework
QoL	Quality of Life
R&D	Research and development
RCP	Royal College of Physicians
RCT/s	Randomised controlled trial/s
RR	Relative risk
RRR	Relative risk reduction
SD	Standard deviation
SEP	Sexual Encounter Profile diary
SERM	Selective oestrogen receptor modulator
SIGN	Scottish Intercollegiate Guidelines Network
Sil	Sildenafil
SPC	Summary of product characteristics
TA	Technology appraisal (NICE)
Tad	Tadalafil
TC	Total cholesterol
TIA	Transient ischaemic attack
TD	Tardive dyskinesia
TG	Triglyceride
T-score	Skeletal mass given as standard deviation units away from the mean value for a young healthy population
TURPS	Transurethral resection of the prostate
UK	United Kingdom
UKCRC	UK Clinical Research Collaborations
UKMi	UK Medicines Information
UN	Units (equivalent to number of packs in DDD calculations)
USA	United States of America
Var	Vardenafil
WHO	World Health Organization
Yrs	Years
Z-score	Number of standard deviations by which the patient's BMD differs from the mean BMD for subjects of the same age/sex

CHAPTER 1

INTRODUCTION, BACKGROUND AND THESIS STRUCTURE

1.1. Introduction

1.1.1. Nature of the Problem

Around 25 new pharmaceuticals are launched onto the market each year in the UK (Light and Lexchin, 2012; Naci *et al*., 2012). Some will be adopted rapidly into use, while others may take significantly longer. But what are the factors that determine whether pharmaceuticals will diffuse successfully or not? There are several bodies of literature including the biomedical, marketing, economics and sociology paradigms that have examined this question specifically for pharmaceuticals (for key reviews and articles see Mason, 2008; Chauhan and Mason, 2008; Atun *et al*., 2007; Prosser *et al*., 2003; Prosser and Walley, 2003a, 2003b and 2005; Jones *et al*., 2001; Hemminki, 1975), and for other innovations within the health care context (Robert *et al*., 2008; Greenhalgh *et al*., 2005; Berwick, 2003; Fitzgerald *et al*., 2002; Bonair and Persson, 1996). However, the emphasis has been on addressing this issue mainly from the perspective of adopter stakeholders i.e. prescribers, payers and policy makers.

While findings for one drug may not be generalisable to others, the one factor that is consistently identified as being influential on pharmaceutical diffusion (both through health professionals' self-report and through correlation with independent prescribing data) is the driving impact of the activities of the pharmaceutical industry (Spurling *et al*., 2010; Prosser *et al*., 2003; Prosser and Walley, 2003a and 2003b; Jones *et al*., 2001; Wazana, 2000; Booth-Clibborn *et al*., 2000; Peay and Peay, 1994; Avorn *et al*., 1982).

Collier and Iheanacho (2002) stated that “via their promotional and educational activity, the pharmaceutical industry is probably the biggest individual influence on prescribing practice”. This view was echoed by Dr Richard Horton, editor of The Lancet, describing that “at almost every level of NHS care provision, the pharmaceutical industry shapes the agenda and the practice of medicine” (House of Commons Health Committee, 2005).

The question of what factors determine the successful uptake of a drug is perhaps of greatest significance to the pharmaceutical industry themselves (to be referred to from here on in as ‘the Industry’), as an understanding and awareness of these factors will inevitably enhance the market potential of their drugs. The competitive edge afforded by such an insight has resulted in little of this knowledge being explicit for fear of revealing marketing strategies. In the absence of that ‘voice’, the Industry’s own activities can provide some insight by being considered a response to the factors they have identified as being important in diffusion, and as such can act as a proxy for reflecting their perspective.

Industry activities have been given significant attention in the biomedical literature over the last decade. The British Medical Journal (BMJ) dedicated an entire issue in 2003 to the Industry’s influence on prescribing behavior. This was followed by a House of Commons Health Committee (HCHC) Inquiry into the Influence of the Pharmaceutical Industry in 2005. There are varying views amongst health professionals as to the impact Industry activities have on the diffusion of drugs. Equally, assessing what the Industry does (or does not do) is merely a reflection of the aspects of diffusion they have influence over. It is therefore worthwhile to seek empirically the views of the Industry directly, not only to validate these findings, but also to explore their implicit views on

other factors they perceive to be important that are outside of their control and subsequently have not been elucidated through their actions.

1.1.2. Purpose of the Ph.D.

This Ph.D. is an exploration of pharmaceutical industry perspectives on factors they think are influential in affecting the diffusion of drugs in the UK through a case study approach. The participating companies are predominantly from the group colloquially known as 'Big Pharma' and therefore the views represent only a subsector of the pharmaceutical industry (limitations are discussed in section 3.8.3). As the 'change agents' responsible for driving the adoption and diffusion of pharmaceutical innovations, the Industry are critical players holding a unique position in gaining a greater understanding of this process. While diffusion curves representing drug usage can show *how* drugs diffuse, the opportunity to speak directly with personnel currently working within the pharmaceutical industry about specific cases aims to provide an insight into the reasons *why* the curves are the shape they are from their perspective. The 'why' questions that increase understanding of the motivations for adopting an innovation have, according to Rogers (1995), only seldom been probed by diffusion researchers.

Through elicitation of common themes across case studies, the intention is to generate a framework of diffusion influences representing an alternative stakeholder's contribution that has been largely absent from the diffusion of innovations theoretical framework. In a comprehensive systematic review of the diffusion of innovations literature in health service organisations by Greenhalgh *et al*. (2005), the authors recommended the need

for further qualitative research on the roles of change agents (individuals who influence client's innovation decisions in a direction deemed desirable by a change agency) in different organisational contexts and settings. The barrier to this type of research however, is often due to difficulties in gaining access to this group of participants.

With the growing focus in the NHS to recognise the benefits of strengthening partnerships with health technology industries with regard to innovation, an appreciation of the issues faced by those driving the diffusion of new technologies, to complement the widely documented views of adopters, will not only enrich the theoretical understanding of this process, but may also provide a platform from which all stakeholders can feel engaged.

1.2. Background

The following section outlines the salient characteristics of one of the most established theories on Diffusion of Innovations and is intended as background information to place the research subject in context.

1.2.1. Rogers' Diffusion of Innovations Theory

> ***"Diffusion is the process by which an innovation is communicated through certain channels over time among the members of a social system."***
>
> ***Everett Rogers, 1962***

Diffusion of Innovations Theory is a mid-range theory that explains how new technologies or ideas are adopted by a population in a predictable pattern. Everett

Rogers' classic text, *The Diffusion of Innovations,* has over several editions summarised and interpreted decades of diffusion research spanning multiple research disciplines to identify basic patterns, categories of adopters, and factors that influence the decision to adopt (Rogers, 1995).

Diffusion is a process of social change that starts with a slow initial (lag) phase, followed by acceleration (take-off) in the number of people adopting an innovation in each time period, then a corresponding deceleration and finally a tail off phase as the last few individuals who are going to adopt finally do so. The bell-shaped diffusion curve becomes an S-curve when cumulative adoption is used (Figure 1.1) (Greenhalgh *et al*., 2005). 'Adoption' describes the "decision to make full use of an innovation as the best course of action available" at an individual level, rather than an aggregate market process (Rogers, 1995).

Some researchers in this field make a distinction between the processes of *diffusion* and *dissemination*, claiming that diffusion is "a passive phenomenon of social influence" compared with dissemination which is an "active and planned effort to persuade a target group to adopt an innovation" (Greenhalgh *et al*., 2005; Mowatt *et al.* 1998). Rogers' definition of diffusion includes both the planned and the spontaneous spread of new ideas, which I perceive to be a more realistic definition of the process, certainly within the context of pharmaceutical diffusion. Seldom, if indeed at all in our current society, can an innovation diffuse in isolation of some 'pushing' influence advocating its use. The awareness of commercially produced innovations is driven by manufactures through promotional efforts during the initial stages, even if at later stages of the process the message takes on a more socially influenced spread amongst individuals. In this particular research context, the diffusion of new pharmaceuticals in isolation of

dissemination is highly implausible, as there will be a manufacturer promoting the use of the drug, certainly throughout its patented lifecycle. Sometimes dissemination efforts may be more subtle when operationalised through influence on guidelines or policy. One could argue that the penetration of pharmaceuticals in the marketplace is purely a process of dissemination, but Rogers' definition does incorporate the more socially driven transfer of information, capturing the exchange that occurs between clinicians and patients once an innovation has been introduced. Even in those circumstances where a pharmaceutical has lost its patent protection many decades ago but for which new indications have been identified, such as with aspirin, there will be a driving influence not necessarily from manufacturers, but from interested parties such as clinicians or policy makers for its use.

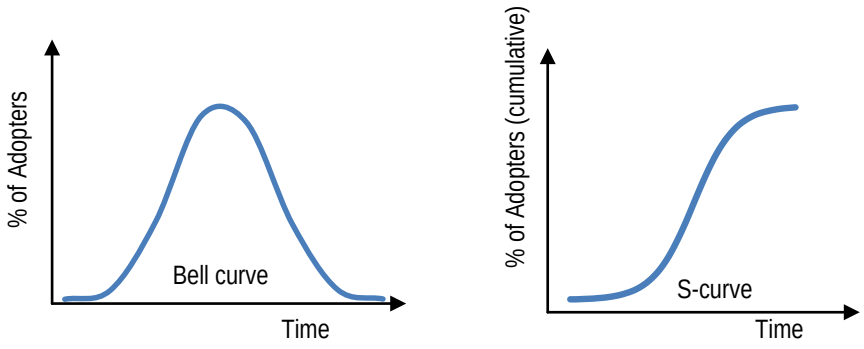


Figure 1.1: The classic S-shaped diffusion curve of Rogers' Diffusion of Innovations model

While there is variation in the slope of the curve from innovation to innovation, the 'take off' phase usually occurs at around 10-25% adoption, when interpersonal networks become activated so that a critical mass of adopters begins to use an innovation. Eventually the trajectory of adoption starts to level off as fewer individuals

remain who have not yet adopted the innovation. Rogers' definition includes four key components: the innovation; the actors who adopt the innovation; the environment into which the new product diffuses; and the means by which the messages are communicated. These four components are briefly outlined in Figure 1.2.

1.2.2. Pharmaceutical Diffusion

Pharmaceutical marketers have traditionally relied on Rogers' model to understand and manage market penetration of a new drug (Kroes *et al*., 2011) and yet the concepts and theoretical explanations of this model are strongly rooted in consumer markets across several research traditions from rural sociology to marketing and economics (for a comprehensive review see Greenhalgh *et al*., 2005). However, while the innovation may differ across these disciplines, the common denominator is the consistent manner in which members of a social system behave (key components of Rogers' diffusion of innovations theory are outlined in Figure 1.2). Early research in pharmaceutical diffusion found Rogers' model to be consistent for drugs, with doctors displaying the same characteristic patterns of uptake as Rogers' adopter categories (Coleman *et al*., 1966; Greer, 1988), however more recent studies have found discrepancies with the model in drug innovation (Kozyrskyj *et al*., 2007; Greenhalgh *et al*., 2005; Dybdahl *et al.* 2004; Peay and Peay, 1994). Wolfe (1994) argued that highly generic and linear models of diffusion utilising the five-stage model of the innovation decision process of knowledge; persuasion; decision; implementation and confirmation (Rogers, 1995) lack empirical validity in pharmaceuticals. This position was supported by Kroes *et al*. (2011) who also argued the Rogers' model has little empirical support in the complex, professional, decision making process typical of pharmaceutical markets.

Figure 1.2: Key Components of Rogers' Diffusion of Innovations Theory

INNOVATION ATTRIBUTES

1. RELATIVE ADVANTAGE
The degree to which an innovation is perceived as better than the idea it supersedes (measured in economic terms, social prestige, convenience or satisfaction). Objective advantage is not necessarily of great importance. The greater the perceived advantage, the more rapid its rate of adoption.

2. COMPATIBILITY
The degree to which an innovation is perceived as being consistent with the existing values, past experiences and needs of potential adopters.

3. COMPLEXITY
The degree to which an innovation is perceived as difficult to understand and use. New ideas that are simple to understand are adopted more rapidly than innovations that require the adopter to develop new skills and understanding.

4. TRIALABILITY
The degree to which an innovation may be experimented with on a limited basis. An idea that is trialable represents less uncertainty to the individual who is considering it for adoption.

5. OBSERVABILITY
The degree to which results of an innovation are visible to others. Such visibility stimulates peer discussion of a new idea.

ADOPTER CHARACTERISTICS

1. INNOVATORS (2.5% of adopters)
Interact with other innovators, educated, venturesome, cosmopolite, risk-taking, information seeking, with a higher financial status.

2. EARLY ADOPTERS (13.5%)
Social, greatest degree of opinion leadership, respected by other members of the social group, adopt new ideas early but carefully. Strategies with a motivational emphasis may be most effective at getting them involved in the diffusion process.

3. EARLY MAJORITY (34%)
Deliberate, adopt new ideas just before the average member of a system, rarely leaders but have many informal social contacts.

4. LATE MAJORITY (34%)
Sceptical, traditional, adopt new ideas just after the average member of a system. The pressure of peers is necessary to motivate adoption. Intervention strategies that help them to overcome barriers are needed to get them to take up the innovation.

5. LAGGARDS (16%)
Traditional, last in a social system to adopt an innovation, pays little attention to the opinions of others. Suspicious of change. Adopts an innovation only after it has taken on a measure of tradition itself.

COMMUNICATION CHANNELS: CHANGE AGENTS

1. DEVELOP A NEED FOR CHANGE
Help clients to become aware of the need to alter their behaviour. They assess a client's need and may help create need.

2. ESTABLISH AN INFORMATION EXCHANGE RELATIONSHIP
Develop client rapport. Enhance relationships by being perceived as credible, competent and trustworthy and by empathising with the client's needs and problems. Innovations are judged on the basis of how the change agent is perceived (accepting the change agent before they will accept the innovation they are promoting).

3. DIAGNOSE PROBLEMS
Analyse client problems to determine why existing alternatives do not meet their needs.

4. CREATE AN INTENT IN THE CLIENT TO CHANGE
After exploring various avenues of action to achieve the client's goal, seek to motivate the client's interest in the innovation.

5. TRANSLATE THE INTENT TO ACTION
The change agent can operate only indirectly, by working with opinion leaders to activate near-peer networks.

6. STABILISE ADOPTION AND PREVENT DISCONTINUANCE
Reinforce messages to clients who have already adopted, thus 'freezing' the new behaviour.

7. ACHIEVE A TERMINAL RELATIONSHIP
A change agent's end goal is to develop self-renewing behaviour on the part of the client (seek to put themselves out of business by developing the client's ability to be their own change agents).

ENVIRONMENT

CENTRALISED: Top down diffusion from R&D through change agents via opinion leaders to adopters.

DECENTRALISED: Innovations spread by horizontal networks among peers and reinvented by other adoptors.

1.2.2.1. Pharmaceutical diffusion: key points of divergence from Rogers' model

The pharmaceutical market has distinct differences from a traditional consumer goods market in several of these key components:

a) Innovation

- Even in the era of evidence-based medicine, when clinicians prescribe drugs, the decision may be affected by factors unrelated to the pharmaceutical properties of the drug.
- Unlike many consumer goods, pharmaceutical product characteristics mean very little without information on what the product does.
- Pharmaceuticals carry a greater element of risk (or perceived risk) than consumer products and therefore ethical, regulatory and liability considerations are often much higher.
- The arrival of imitators is a more controlled phenomenon in medicines than consumer markets.

b) Adopters

- A key difference in medicine is that the consumer (patient) is neither the decision maker, nor the buyer. The new product must be adopted first by the clinician before it can be adopted by the patient. Aggarwal and Cha (1997) suggest the term 'surrogate adopters' to describe the role of clinicians as they occupy a unique position. They act both as gatekeepers by selectively choosing which innovation to adopt based on their own values, and as facilitators in diffusing the new product among patients.

- Clinicians use more nebulous criteria for judging the efficacy of an innovation compared with commercially driven criteria (Fitzgerald *et al*., 2002).
- Clinicians do not always follow the Rogers' model of 'adopter categories' i.e. innovator behaviour is not consistent with all new technologies (Jones *et al*., 2001; Greenhalgh *et al*., 2005).

c) Environment

- The market for innovative drugs is the NHS, which is a very different environment in which to operate compared with consumer markets. In terms of drug innovations, the NHS represents a centralised system involving multiple stakeholders, which places a far greater importance on the interactions between groups. Since its inception in 1948, the NHS has taken on many structural forms, each iteration bringing with it a change in the degree of influence of different stakeholder groups in the process.
- The Industry operates within a highly regulated environment in the way it undertakes research, produces and licenses its products, creating more hurdles than in consumer markets. This has prevented predictive models of diffusion such as the Bass model[1] (a mathematical presentation of the Rogers' model), which in consumer markets has provided a means for marketers to predict whether, and to what extent, a particular innovation would 'catch on', from being widely used in health care diffusion research (Sillup, 1992).

[1] The Bass model assumes that new product adopters are influenced by two types of communication: mass media and interpersonal communication, and that the mass media effects, which have a greater impact on innovative customers, will be greater at the outset of the product launch. The interpersonal communication effects, which have a greater impact on the much larger number of imitative customers, will be greater during the later periods of the diffusion process (Rogers, 1995).

- Whilst individual doctors retain clinical freedom to treat patients as they deem appropriate, there is increasing pressure from managers, prescribing advisors and payers that has created a 'comply or explain' philosophy in an attempt to control the medicines bill. Limited formularies, incentives to encourage generic prescribing and formal assessments of the clinical and cost effectiveness of new medicines have been the environment in which prescribing decisions have been made.
- There is an implicit social incompatibility between profit and health, giving rise to negative connotations with regard to marketing and promotional activities in medicine, which does not affect most consumer goods markets.

d) Communication channels

The role of the Industry as the 'change agency' is not only to produce innovations, but also to communicate information about them. Marketing, which is the process responsible for anticipating and satisfying customer requirements profitably (UK Chartered Institute of Marketing), and opinion leadership, which utilises the influence of revered experts are based on central communication aspects of Rogers' model. However:

- pharmaceutical change agents are more likely to be homophilous with clinicians in social characteristics, thereby avoiding the social marginality Rogers refers to that can otherwise present a communication barrier for change agents in commercial markets. They are however, heterophilous with regard to technical competence about the innovation being diffused, affording them an educational role. Greenhalgh *et al*., (2005) highlighted that within the medical profession

change agents naturally focus their efforts on innovators and early adopters because they tend to share more characteristics with them, however they argue their input is most needed for late adopters.

- pharmaceutical change agents do not withdraw from the market as suggested by Rogers when a critical mass is reached at around 30% adoption. They continue to influence behaviour throughout the patented lifecycle of a drug.

1.2.3. The Pharmaceutical Industry

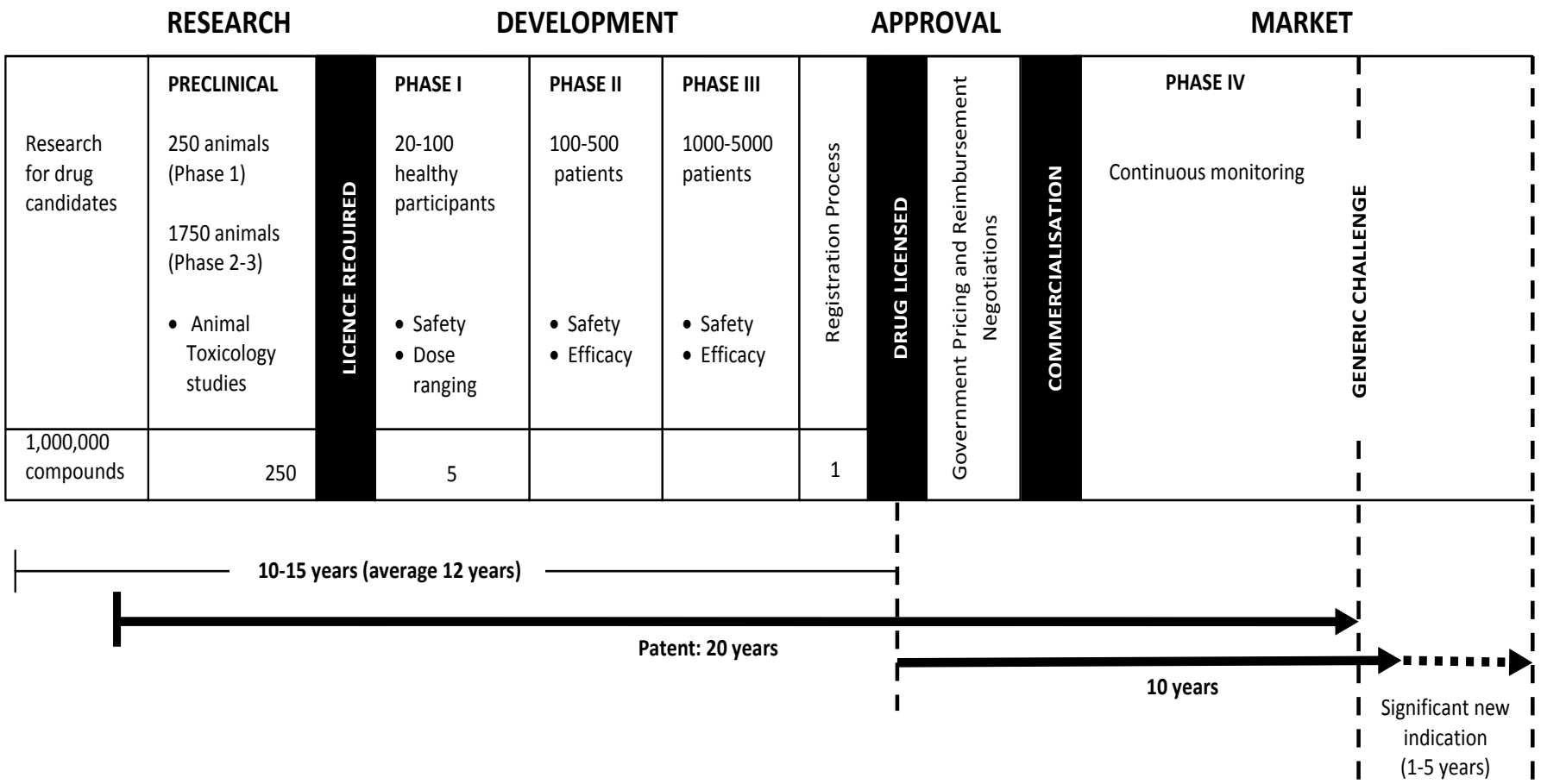
The pharmaceutical industry represents the UK's third most profitable economic sector and employs around 80,000 people directly and around 250,000 as a result of the Industry's presence in the UK. It is therefore of significant importance to the UK economy. The purchase of medicines accounts for around 12% of the entire NHS budget, with total drug sales to the NHS in 2011 of £13.7 billion (Association of the British Pharmaceutical Industry (ABPI), 2012a). The UK represents around 7% of world sales after the United States of America, Japan, Germany and France, and has traditionally been an important site for drug-related research and development. With such an economic presence, the Government has to balance the need to promote the competitiveness of the Industry, with the need to address health concerns and promote the effectiveness of the NHS (HCHC, 2005).

It is important to recognise that the pharmaceutical industry is not just one organisation. It includes companies that focus on research and development of new pharmaceuticals, biotechnology companies, generics companies, and companies that combine new drug development and generics. While they all share a common purpose to manufacture,

supply and market medicines, each of these different business models will hold different beliefs around what affects the diffusion of pharmaceuticals based on their own individual challenges. The dominance of a small number of large multinational companies (colloquially known as 'Big Pharma') indicates the high level of inherent risk that accompanies research and development of new pharmaceuticals. The reported costs of drug development are now in excess of £1.2 billion due to the high attrition rates that result in only one drug launched for every five to ten thousand compounds evaluated. Patent life is typically around 20 years, of which around 12 years is taken up by the drug development process (outlined in Figure 1.3).

During the course of the drug lifecycle, the Industry interacts with the health system in two ways; i) through research and development and ii) drug promotion and advertising, the first being more comfortably acknowledged by health professionals according to Breen (2004). Once launched, a drug is subjected to further evaluation through post-licensing surveillance by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Yellow Card Scheme for adverse reactions, and through bodies such as the National Institute for Health and Clinical Excellence (NICE) that assess clinical and cost effectiveness.

Figure 1.3: The Drug Development Process (adapted from the Nuffield Council on Bioethics report, 2005)



A key concern of the Industry is the rate at which new technologies are adopted in the UK, which is amongst the slowest in Europe (Wanless, 2002; Danzon and Kim, 2002) and has been attributed to the conservatism of prescribers (Griffin, 1995) and regulatory hurdles such as NICE. The UK adoption rate measured as mean per capita use, is 54% of average international levels 5 years after product launch (Pharmaceutical Industry Competitiveness Task Force (PICTF), 2005). The Industry's aim through its activities is to accelerate the uptake rate of their products in the initial phase, and ensure that the product is adopted by the maximum number of prescribers during its remaining patent life.

The pharmaceutical industry is now considered to be a matured market, demonstrated by traits such as decreasing product differentiation, industry consolidation, slower rate of growth and intensifying competition. Mature markets favour expertise in market strategy development (marketing), compared with growing markets that favour product development skills (innovation) (Smith, 2003a), which is in accordance with the perception held by critics of the Industry in relation to where their priorities are focussed.

1.2.4. Industry Activities

There is little doubt that Industry activities have the ability to influence prescribing decisions, with a substantial number of articles published in the biomedical literature assessing the impact of such influence (Spurling *et al*., 2010; Watkins *et al*., 2003; Prosser *et al*., 2003; Prosser and Walley, 2003a and 2003b; Wazana, 2000; Chren and Landefeld, 1994; Lexchin, 1993). The BMJ Industry-themed issue in 2003 (volume

326) focussed on disentanglement of doctors from drug companies, while the parliamentary inquiry found some questionable Industry practices, with assertions of buying influence over doctors, researchers, patient groups, charities, journalists and politicians. Regulation provided by the MHRA was regarded as being weak or ambiguous stemming from a culture of common policy objectives, consultation and interchange of staff with the Industry, which was exacerbated by the need for competition with other regulators in Europe (HCHC, 2005). These issues are not new, but their significance has increased in parallel with the Industry's increasing size, influence and power.

The strategies used by companies to increase awareness of new drugs amongst stakeholders (most notably prescribers) are diverse and wide reaching. Overt practices include visits by drug company representatives (Naik *et al*., 2010; Manchanda and Chintagunta, 2004; Prosser and Walley, 2003a; Jones *et al*., 2001; Buban *et al*., 2001; Pugh *et al*., 2003), advertisements and advertorials (Smith, 2003b; Jones *et al.* 1999; Walton, 1980), direct mailing (Collier and Iheanacho, 2002), free samples and gifts (Wazana, 2000; Katz *et al*., 2003; Brett *et al*., 2003), and sponsorship of meetings and conferences (Heath, 2011). These activities are regulated under the ABPI Industry Code of Practice, which is policed by the Prescription Medicines Code of Practice Authority, although implementation of the Code is sometimes perceived as unsatisfactory (Dowsett *et al*., 2010).

More covert influences reported in the literature include Industry links with regulatory authorities (Abraham, 2002; Hemminki, 1980), scientific investigators and academic institutions (Psaty and Rennie, 2006; Bekelman *et al.*, 2003; Boyd and Bero, 2000), guideline producers and patient groups (Choudhry *et al*., 2002; Henry *et al*., 2005;

Herxheimer, 2003), use of opinion leaders to convey Industry views (Liberati and Magrini, 2003; Jackson, 2001; Minhas, 2007), provision of continuing medical education to prescribers and medical students (Zipkin and Steinman, 2005; Sandbery *et al*., 1997; Relman, 2001), the invention of new diseases to match their pipelines (disease mongering)' (Moynihan *et al*., 2002), and while 'direct to consumer' advertising is not permitted in Europe, disease awareness programmes and use of the mass media provide a conduit through which to influence patient perceptions (Burton and Rowell, 2003; Collier and Iheanacho, 2002).

Furthermore, scrutiny of Industry funded trial publications has also led to allegations of the Industry withholding negative findings from publication (McCarthy, 2000; Nathan and Weatherall, 1999), selectively reporting favourable outcomes (Spurling *et al*., 2010; Lexchin *et al*., 2003; Bhandari *et al*., 2004; Bero and Rennie, 1996), bias in trial design (Rochon *et al*., 1994; Montaner *et al*., 2001) and paying non-Industry experts for engaging in ghostwriting and guest authorship (Dowsett *et al*., 2010; Moynihan, 2003). While many of these sources are from the USA, pharmaceutical companies operate at a global level, therefore with the exception of direct to consumer advertising, many of the issues raised in articles by international authors are also relevant to the UK.

There are divergent views amongst clinicians about the value of the information provided by pharmaceutical companies, with arguments on both sides increasingly appearing in the literature. Studies have shown that some see the information provided by companies as useful, especially in the immediate post-launch phase (Fischer *et al*., 2009; Chimonas *et al*., 2007; Prosser *et al*., 2003; Prosser and Walley, 2003a; Azoulay, 2002; Jones *et al*., 2001; McGettigan *et al*., 2001; Wieringa *et al*., 2001; Gönül *et al*., 2001; Huston, 1993), whilst others refute any influence, or believe it may affect their

colleagues but not themselves (Morgan *et al*., 2006; Rutledge *et al*., 2003; Watkins *et al*., 2003; Steinman *et al*., 2001; Carthy *et al*., 2000; Chren, 1999; Peay and Peay, 1988; Avorn *et al*., 1982). What is clear, however, is that many doctors are willing to give time to Industry representatives (Blumanthal, 2004). There is also some evidence that because of misleading promotion leading to poor clinical practice (Othman *et al*., 2009; Montgomery *et al*., 2008; Lexchin, 1997; Ziegler *et al*., 1995; Hemminki, 1977; Spurling *et al*., 2010; Wazana, 2000), a number of organisations have called for the stricter control of Industry activities (Rothman *et al*., 2009; Mansfield *et al*., 2006).

1.3. Chapter comment

The Industry, with regard to how it operates, is not well understood by those outside of it. The knowledge they possess on the diffusion of pharmaceuticals is of considerable value to complement various other stakeholder perspectives in the pursuit of a balanced view of this sociological process. Greenhalgh *et al*. (2005) identified that "whilst there is a wealth of empirical research into the role of change agents in general, the literature into the role of change agents in disseminating innovations in health service delivery and organisation was sparse". The following research project has sought to elucidate and present Industry views on what factors from the perspective of the change agent affect drug adoption and diffusion rather than relying on proxy measures of their activities. Through this exploration, their role in the process is also revealed.

1.4. Thesis structure

Chapter 2 presents a review of the current literature addressing Industry views on diffusion influences, directly or through empirical research.

Chapter 3 provides an overview and rationale of the methods of research and analysis selected and considers some of the practical considerations for undertaking data collection in this context. This section concludes with a discussion of the strengths and limitations of the research, taking into consideration quality assessment measures commensurate with qualitative research i.e. credibility, dependability and transferability of the findings.

Chapter 4 presents the data portfolios for each of the four case studies including the diffusion curves and the case specific literature and clinical expert augmented timelines with accompanying commentaries.

Chapter 5 presents an across case study thematic analysis of the Industry interviews, identifying a framework of Industry perceived factors that influence the diffusion of pharmaceuticals.

Chapter 6 explores through triangulation the degree of convergence and divergence between the diffusion curves, Industry respondents and literature-based accounts for each case study, which served to test the validity of the data and elucidate unique Industry insights.

Chapter 7 outlines a discussion of the main findings and implications of the research. This is accompanied with a reflection on what further research may be supported in view of the conclusions.

CHAPTER 2

LITERATURE REVIEW ON PHARMACEUTICAL INDUSTRY PERSPECTIVES

2.1. Introduction

The aim of the literature review was to determine the extent to which the views of the Industry on diffusion influences have been previously elucidated in the literature, either directly through Industry authored pieces, or indirectly through empirical studies with Industry personnel as the subject of the research. While it is acknowledged that there is a wealth of literature from many other perspectives that may oppose these views, it was not within the scope of the literature review to address these as the intention was to find out the ideas and opinions of Industry respondents.

2.2. Search methods

The topic spanned multiple research disciplines and required extensive searching of both the peer-reviewed and grey literature across seven databases applicable to the biomedical, social sciences, business, law and economics fields, dating from their inception through to September 2012 (see Appendix 1 for details of databases searched and search strategy employed). As this qualitative inquiry was concerned with uncovering the Industry's own voice, normative literature was not included, as its authorship was dominated by consultancies or marketing academics rather than Industry contributors. No studies were identified that directly addressed the research question

that was intended to explore the importance of multiple rather than single diffusion factors, or to such a comprehensive extent as afforded by the case study approach.

2.3. Diffusion themes from Industry authored commentaries

The literature surrounding the topic of the pharmaceutical industry is plagued with seemingly biased contributions from both critics of the Industry and the Industry themselves. Indeed the stimulus for many of the Industry authored articles has been their need to counter accusations about their practices and influence, some based on robust studies, but often characterised by polemic. There is little doubt that the Industry can influence prescribing decisions. They present themselves, and wish to be considered very much as partners in the healthcare system (Barr, 1994), which rightly or wrongly is reliant on their resources for research, education and delivering patient benefit through pharmaceutical innovation. Through general discussions of specific aspects in the literature, several factors were revealed by Industry contributors as potential influences on diffusion, which are outlined below.

2.3.1. Diagnosis

The Chief Executive Officer (CEO) of Roche in 2004 described how diffusion of new drugs is dependent on patients coming into the system to be treated through accurate diagnosis. Conditions for commercial success include symptoms that are readily identifiable and measurable so that clinical response can be monitored (Humer, 2004; Alphs, 2006). Townsend (2011) and Knowles (2011) discussed how diseases that are

difficult to define as a result of their complex aetiologies, such as Alzheimer's disease and severe asthma, present delays to completion of clinical trials e.g. in terms of patient recruitment; determining appropriate outcomes measures; lack of surrogate measures and the impact that has on extending trials. Additionally primary care physicians are not necessarily equipped to make such highly accurate diagnoses, particularly as simple tests are unlikely to be available. Without a diagnosis, or the availability of the necessary provisions to make a diagnosis, the Industry has highlighted how this is a barrier to the dissemination of any new treatment.

The Industry has faced criticisms in relation to disease redefinition, which involves widening diagnostic boundaries of conditions to increase the eligible patient population (Moynihan *et al*., 2012). The Industry argues that the criteria by which patients gain inclusion for treatment in the UK are set through government and professional guidelines, such as the National Service Frameworks (NSFs) and the General Practice Quality Outcome Frameworks (QOF). A former medical director of the ABPI acknowledged however, that the Industry is involved in "sponsoring the definition of diseases in conjunction with regulatory authorities to develop closely defined definitions such that safety and efficacy of new medicines can be properly measured" (Tiner, 2002).

An example of disease classification that was surrounded with controversy was the WHO definition of osteoporosis. The primary concern from critics related to the emphasis on the importance of bone mineral density (BMD), a surrogate marker. By raising BMD to the status of a diagnostic criterion, it conceptualised a risk factor as a disease (Eastell, 1998). This is a concern with surrogate markers in general and ultimately their ability to translate to clinically relevant endpoints. The fact that the

WHO definition set the bone density of young white women as normal, and to judge the bones of older women against this standard was also viewed contentiously by some in the medical profession, who have indicated a Z-score measure (BMD is compared with the mean value in normal subjects of the same age and sex) may have been more appropriate (Eastell, 1998; Moynihan *et al*., 2002). Some have implied that interested companies were heavily involved in influencing the WHO definition, through sponsorship of key meetings of the WHO study group, and developing extensive financial ties with leading researchers and patient groups (Moynihan, 2002).

2.3.2. Research and Development (R&D)

Genuine innovations

Even in small patient populations, some Industry authors believe there can still be significant commercial opportunity if an innovation is addressing an unmet need (Knowles, 2011; Antonaccio, 1994). The Industry have not disputed that they are financially obligated to their shareholders, but as that profit can only come to fruition by satisfying clinical need with innovative drugs that improve the quality of healthcare, this does not automatically put them at odds with the priorities of Government and health professionals (Leather and Davis, 2005; HCHC, 2005; Blackledge, 1999).

To identify areas of unmet clinical need, Robinson (2000) discussed how the Industry uses epidemiology to guide their research agendas, by providing information on the extent and severity of disease in different populations and the burden on resource use. The traditional model of pharmaceutical R&D has been to discover new drug candidates in-house, but in the wake of stagnating pipelines, companies have used various strategies to increase their access to new products and new research. This has been

achieved through mergers and acquisitions (Gopal, 1998; Mittra, 2007), strategic alliances and collaborative research efforts (Spiegel, 1991; Cagle, 2005) or new R&D models such as GSK's Centres of Excellence for Drug Discovery (CEDDs). CEDDs are based on a configuration of seven units designed to encourage competition between the company's researchers according to therapeutic area to stimulate development of innovative products (Iglehart, 2003).

Meeting an unmet need may not require radical innovations. Incremental developments are usually regarded by critics as strategies to extend patent protection but, as Tom McKillop (CEO of AstraZeneca in 1998) highlighted, companies get the product to market "as quickly as possible for a defined indication and then look for ways to add value to that product". That value may not be identifiable until the drug has been in use for some time and may involve developing a new formulation for example, but if this modification addresses a problem that has been preventing patients from using a medication then its impact on diffusion can be significant (Gopal, 1998).

Critics of the Industry however, have concerns that needs are being invented in accordance with a company's existing portfolio of drugs. This practice, which is referred to pejoratively as 'disease mongering', involves the medicalisation of ordinary life, such that the "social construction of illness is being replaced by the corporate construction of disease" (Moynihan *et al*., 2002; Moynihan *et al*., 2012; Goldacre, 2012). Examples often cited include female sexual dysfunction, menopause presented as hormone deficiency and shyness as social anxiety disorder. In response to this issue, the Industry indicated in their evidence to the HCHC Inquiry that a drug can only be licensed for a valid condition that is internationally recognised through the WHO International Classification of Diseases (ICD) system. However, as indicated in section

2.3.1., the Industry has made acknowledgements in the literature of their involvement in the definition of diseases.

UK research presence

Around one fifth of the most commonly prescribed drugs used worldwide were developed in the UK (ABPI, 2012b). The Industry claim it has become increasingly expensive to conduct clinical trials in the UK and that an uncompetitive environment, with the loss of UK research presence, could detrimentally impact on drug diffusion. By retaining research in the UK, clinicians and patients can input into research priorities, keeping UK physicians at the forefront of clinical research and enables patients to access new medicines through clinical trials (HCHC, 2005). PICTF was a joint initiative between the UK Government and the Industry with the aim to ensure the UK remained a desirable location to conduct research, and the NHS as a setting to run clinical trials (PICTF, 2001). While it is claimed that the UK's reputation for scientific and clinical innovation is threatened by expertise of the emerging world, the high quality standards of UK research, the unique patient and staff resource provided by the NHS and recent initiatives such as the UK Clinical Research Collaboration (UKCRC) and the NIHR Clinical Research Network (NIHR CRN) is likely to mean that the UK will remain an attractive proposition for the Industry.

Forecasting R&D priorities

Increased regulatory requirements have had a significant influence on the financial risk to companies by increasing the cost of drug development and reduction in patent life. It is estimated that fewer than one in five new drugs recover the cost of their development (Macdonald, 1990). A challenge for companies is that they have to make key development decisions with no certainty of what the market conditions will be like at

launch with regard to clinical priorities and competitors. Misjudgement of these predictions can have major consequences on the diffusion of a drug. Determining the needs and priorities of stakeholders, both clinical and financial through market research activities, can help mitigate the risks involved in these forecasting decisions, leading to the development of a drug that can be differentiated both on its clinical and commercial attributes when it eventually reaches the market (Alphs, 2006). As mentioned in previous sections, this view is in contrast to that held by Industry critics who believe that needs are not necessarily congruent with those of stakeholders.

2.3.3. Medical research/Clinical trials

Clinical trials serve an important function in diffusion; they provide the evidence to allow a drug to enter the market, but are also used to communicate information about the risks and benefits of new therapies to decision makers and prescribers to change clinical practice. They also substantiate the Industry's education activities by providing legitimacy to their claims (Cappelleri and Stecher, 2008; Marlow, 1994).

2.3.3.1. Trial design barriers

Regulatory constraints

The appropriateness of clinical trial design is a common criticism of Industry funded trials, the suggestion being that the design intentionally shows the drugs in the most favourable light. The Industry response is that medicines are produced as part of a global strategy, and so comparators may not always be applicable to every country. The intended impact of a trial may be lessened if some countries claim the results are

inconclusive. Companies therefore have to ensure that trial design will accommodate the needs of regulatory agencies and clinicians in various countries as much as possible, but the constraints of regulation can often frustrate clinical investigators and assessors (Blackledge, 1999; Carmine, 1996).

Restricted trial population

Clinical trials are usually conducted in the secondary care setting under the control of specialists. The patient populations enrolled are governed by strict inclusion and exclusion criteria, which can only therefore provide a limited insight into how the drug will perform in a real world context. There have been some suggestions from Industry that conducting pre-marketing trials in general practice may provide a sample more representative of the vast majority of patients who will use the drug, while also allowing general practitioners (GPs) to be involved in clinical evaluation (Marsh, 1981). Post-marketing studies currently provide this context but they are sometimes viewed as an opportunity to increase product name recognition by recruiting patients via prescribers (Anonymous, 2012).

Double-blind design

The double-blind trial design has been highlighted by Industry authors as being detrimental to the uptake of some new drugs. Its purpose is to reduce differences between treatment or analysis that may confound the interpretation of the results, but in some cases it may lead to the obscuring of possible benefits of new treatments. An example cited by Industry authors Anderson and colleagues (1999) involved the antiplatelet drug abciximab. The drug's relative advantage was its enhanced cost effectiveness resulting from a reduced need for repeat revascularisation during the 6

months after hospitalisation in patients undergoing percutaneous transluminal coronary angioplasty (PTCA) or arthrectomy. In using a double-blind trial design however, the benefit of abciximab was compromised by the need to administer standard dose heparin in all treatment arms to avoid making the treatment arms identifiable, which produced a higher rate of bleeding complications with abciximab. Any early cost benefit that was expected from a reduced need for repeat interventions necessary to offset the upfront costs of the drug was apparently eliminated due to administration of heparin. Despite these possible tensions, the evidence supporting the use of such study designs is overwhelming. While the problems identified in this particular example are not commonly encountered, they should be recognised.

Multiregional trials

The intention of multiregional trials is to accelerate the approval process. A region takes into consideration factors such as race, ethnicity, disease epidemiology, medical practice and geographical proximity. Geography is the most common way of defining a region, but it is not necessarily the most appropriate. For example, the regions defined in the PLATO study, comparing ticagrelor with clopidogrel which included North America; Asia/Australia; Central/South America; Europe/Middle and East/Africa; have been criticised for having little relationship with either practice patterns and/or population genetics. An increasing number of companies have started to conduct late phase trials in emerging clinical trial locations in developing countries, such as Latin America, India, the Middle East, and Africa. Despite the view that Industry are exploiting trial subjects in these regions, the assertion by Industry is that regional variations, caused by the diversity of patients and medical practice, has resulted in

significant debate during the regulatory process, potentially slowing access and reducing confidence in outcomes (Binkowitz and Ibia, 2011).

Comparative effectiveness

Regulatory approval is usually based on randomised, placebo-controlled trials, but more robust comparative trials are becoming necessary for a drug to get through market access hurdles. According to the Industry authored literature this is presenting a significant barrier to adoption. Large scale trials are necessary to attain sufficient statistical power to demonstrate superiority, but they inevitably increase the cost of drug development. This has been raised as an issue of concern as it may discourage future innovation within a class, as benefit is not always a feature of efficacy, but may relate to improvements in tolerability or safety (Yager and Starrett, 2006). Enrichment of trial populations to select those patients most likely to display the outcome of interest may however, mitigate the need for vast trials (Knowles, 2011), but it also increases the chances of obtaining a positive trial outcome. As indicated in the commentary by Berger and Grainger (2010), early engagement with assessment agencies enables companies to discuss design issues to achieve credible outcomes that satisfy the requirements of the assessors and thus minimise potential access barriers.

2.3.3.2. Credibility of Industry funded studies

Publication of trials and economic models in peer-reviewed journals has been highlighted in Industry authored commentaries as being the most credible means of conveying research findings to medical communities (Miranda and Ginestet, 2002; Olson *et al.*, 2003). The vast majority of studies for new drugs are funded by the Industry (approximately 90%) as it is a regulatory requirement for companies to

generate clinical trial data to support their market approvals. In evidence submitted to the HCHC Inquiry, the Industry outlined how they invest £3.3 billion per year (£10 million per day) into R&D in the UK, which exceeds every other public source combined (HCHC, 2005). In the absence of publicly funded studies, Industry funded trials, which account for over three quarters of randomised controlled trials (RCTs) reported in major journals, provide a basis for decision making and are therefore a key factor in diffusion.

However, the premise that Industry funded studies are less credible, which is a view widely presented in the academic literature, has according to Tohen (2007), undermined the impact of genuine scientifically valid contributions. The perception that they cannot be trusted in the same way as the outcomes of non-Industry funded trials, has implications in slowing the rate of adoption. Studies have been conducted showing that trials sponsored by pharmaceutical companies are more likely to have outcomes favouring the sponsor (Lexchin *et al*., 2003; Bhandari *et al*., 2004; Lexchin *et al*., 2010), resulting from selective funding of trials on drugs that the company considers superior to the competition or through design aspects such as inappropriate comparators. Rochon and colleagues (1994) demonstrated that in most cases in which the doses of the study and comparator drugs were not equivalent, the drug given at the higher dose was that of the supporting manufacturer. Additionally, publication bias has been implicated in the disproportionate representation of positive Industry trials, with the suggestion that manufacturers have attempted to prevent studies which are unfavourable to their products from being published (McCarthy, 2000). A counteraction from the Industry literature however, is that in many cases, journals are reticent to publish negative studies.

Tohen (2007) argues that the quality of the findings from Industry supported studies should be judged on the rigour of the scientific methodology rather than the credentials or affiliations of the investigators or the source of funding. In the systematic review by Lexchin *et al*. (2003) highlighting Industry sponsorship and research outcome, none of the 13 studies that analysed methods reported that studies funded by the Industry were of poorer quality. They even went as far as stating that research methods were "at least as good as non-industry funded research and in many cases better".

Dowsett *et al.* (2010) defended the premise that "a conflict of interest does not necessarily equate to a biased representation of research findings" and that "operating a successful, for-profit business and maintaining a focus on improving health are not mutually exclusive goals". In an attempt to redress the balance, several authors (Chavers *et al.*, 2011; Tohen, 2007; Blum *et al*., 1986; Stucki, 1985) have argued that financial conflicts of interest are not the sole source of conflict that investigators may have, with others potentially arising when research outcomes dispute hypotheses, mainstream medical views or a researcher's prior publication record.

Such is the importance of clinical evidence, the Industry are responding to the criticisms that have been levelled at them with regard to overly positive results and poor quality design, through initiatives such as clinical trial registers (Dowsett *et al*., 2010; Norris, 2010; Mansi *et al*., 2012; Leather and Davis, 2005; Chavers *et al*., 2011) and publishing their own publication policies (Dowsett *et al*., 2010), and recommendations for closing the credibility gap in reporting Industry sponsored clinical research (Mansi *et al*., 2012). Some would argue however, that this has taken a concerted effort on behalf of campaign groups such as AllTrials, that call for all past and present clinical trials to be registered

and their results reported in the public domain, to bring about this change in perspective (Coombes, 2013).

2.3.4. Cost impact

The cost of pharmaceuticals is a contentious issue. Coombe (2000) suggested that some doctors do not prescribe certain drugs even though they know they work simply due to cost pressures. Industry authors argue that while pharmaceuticals are considered by Government as the cause of increasing NHS expenditure, they have consistently accounted for between 10-15% over several decades (Wells, 1992), with hospital expenditure accounting for more than 50%. With the removal of waste and unnecessary expenditure in other sectors, the suggestion is that this could produce savings in excess of the total pharmaceutical spend (Griffin and Teeling Smith; 1992). The high cost of drug development is attributed to the inherent risks involved in the R&D process, but the Industry has been keen to highlight that around 17%-25% of sales revenue is reinvested in further R&D efforts, which is more than many other comparable industries (Rajfer, 1993; Iglehart, 2003; Azoulay, 2002). Complex manufacturing methods can further inflate costs as demonstrated in the case of biologics (Kramer, 2011), which can present an adoption barrier for these drugs resulting from the price differential compared with the existing market. Griffin and Teeling Smith (1992) also argue that without premium prices made possible by patents and brand names, there would be no economic motivation for innovation.

The cost stated to bring a new medicine to the market is now in excess of £1.2 billion. While it is acknowledged that the rigorous assessment of medicines is an expensive process and that companies are entitled to expect a return on their investment, health

services have to be confident that the extra benefit to patients justifies the price. Some have started to question this figure, including the chief executive of NICE who in an open letter to The Times newspaper stated “If it really does cost £1.2bn to develop a new drug, the question the pharmaceutical industry must be able to answer is this: are you absolutely confident that it needs to?” (Dillon, 2013). Suggestions have been made that all aspects of the drug discovery and development process including the requirements of the regulatory authorities should be examined for potential cost savings to prevent this estimate from continually increasing (Rawlins, 2004).

The relative advantage offered by many drugs is related to the long-term savings they can provide through prevention (i.e. medications reducing the need for expensive interventional procedures), or impacting on health resources by reducing length of stay. But the perceived high initial costs may present a barrier to diffusion of innovative medicines (Iglehart, 2003). An alternative cost perspective presented by Industry authors Griffin and Teeling Smith (1992) in response to the usual criticism that an over-spending doctor should be discouraged, is that an under-spending doctor is just as much of a problem as they are potentially failing to diagnose and treat conditions in their patients. The premise for this position is that such doctors are often failing to realise the cost savings for the NHS that can come from preventative medicine being correctly implemented. The cost-benefit of preventative medicines is however, difficult to demonstrate, particularly in a medical culture that remains heavily focused on treating rather than preventing disease.

2.3.5. Health Technology Assessment (HTA)

HTA was the focus of many Industry articles (Keech, 2001; Thwaites and Townsend, 1998; Lothgren and Ratcliffe, 2004; Earnshaw and Lewis, 2008). Recent studies acknowledge it has a major role in drug adoption as pharmacoeconomic research assists in decision making, but the earlier empirical studies questioned its value (see section 2.5). The commercial benefit of HTA has been recognised by the Industry in that it can lead to more profitable commercialisation of new drugs through earlier and increased access to customers and markets, with evidence-based justifications and acceptance of possibly premium priced products. Additionally collaboration with HTA submissions can improve a company's reputation and improve relationships with customers through enhanced credibility for their commitment to high quality research and the provision of cost effective healthcare (Thwaites and Townsend, 1998; Berger and Grainger, 2010).

Equally, companies have to balance the ambition to provide more comprehensive information, with the risk that it extends an already lengthy process to market access. Earnshaw and Lewis (2008) commented that while they recognised the need for robustness and quality in NICE guidance, there are equivalent needs of the NHS for timely information and the need of patients for access to new drugs. With a shortened period to recoup investment costs from the pressure of generics, the 'fourth hurdle' as it is often referred to, which requires a new drug to demonstrate economic benefits at national and regional levels in addition to the licensing requirements of safety and efficacy, could reduce this time even further (Lothgren and Ratcliffe, 2004).

Many companies have integrated cost effectiveness measures into the development process at much earlier stages to provide data to agencies ahead of launch, otherwise the

assessment process can cause significant delays to adoption (Keech, 2001; Thwaites and Townsend, 1998). However, there are usually discrepancies between the economic models submitted by the sponsoring companies and the independent analyses conducted on behalf of NICE, which can lead to delays in the process. The robustness of NICE's procedures and the confidence this creates in their outcomes has ultimately increased the promotional impact of a positive NICE recommendation through its ability to accelerate the adoption and diffusion of that drug or its class. It could be inferred therefore to have contributed in part to the Industry's acceptance of the role of HTA in pharmaceutical assessment.

Complexity (Knowledge barriers)

Formal HTA processes have been part of decision making in the NHS for over 10 years. Yet several Industry articles alluded to how some prescribers, formulary managers and policy makers are not comfortable with the principles and methods of economic analysis and may not feel confident to interpret the data contained in these studies (Olson *et al*., 2003; Thwaites and Townsend, 1998; Assiff *et al*., 1999). The fear is that decision makers may become disenfranchised by the highly technical focus of what is otherwise a very useful tool in decision making (Earnshaw and Lewis, 2008). The challenge faced by Industry is to communicate the wider implications of treatment choices to ease the burden of decision making, but some companies felt they were not always meeting the needs of their customers in this respect and that sales forces now need to be competent in this aspect (Armstrong *et al*., 2001; Thwaites and Townsend, 1998). Since some of the earlier articles were published, the growing importance of HTA in decision making in the NHS has meant that this potential barrier, while it may have been plausible at that time, is unlikely to be credible in the current climate. NICE

appraisals are intended to condense the complexities of HTA, such that the findings are transferable to a broad audience of decision makers.

Relevance

NICE has a key role in evaluating the findings of clinical and cost effectiveness analyses and then translating their assessments to key users of that information. Wells (1992) noted however, that economic analyses that take into account impact on all sectors of the health service can be seen by some groups to have only limited relevance to their own activities, which inevitably limits its impact. The view expressed by some Industry authors is that practitioners constrained by budget silos are principally concerned with their drug costs and not explicitly with the resource implications on other parts of the health service. Presenting cost effectiveness data in such a way that has relevance to all concerned parties is difficult as there are differences in the perceptions of costs and benefits depending on who the decision maker is, but customisation inevitably increases the value of this information (Anderson *et al*., 1999; Olson *et al*., 2003). Responding to customer-specific, country-specific, national, and multiregional HTA requirements, while vital in developing effective guidance, contributes to the increasing costs of medicines and can cause delays to access if the prioritisation process and methods of assessment used by HTA agencies are not clearly defined (Lothgren and Ratcliffe, 2004; Schubert, 2002).

2.3.6. Patient influence

Patients and patient groups have been exercising increasing levels of influence in their demands for access, quality and priorities in healthcare. The Industry authored literature accepts this can accelerate the rate of diffusion of a new drug through increasing public

awareness of diseases, particularly in circumstances, as in the UK, where advertising to patients is not permitted (Thwaites and Townsend, 1998; Buttle and Boldrini, 2001; O'Quinn, 2001). Some patient groups receive funding from pharmaceutical companies as there is a vested interest for both parties from such an interaction. There are criticisms however, that pharmaceutical companies and patient organisations are unequal partners in these collaborations, which raises serious questions about the influence afforded to patient groups in decision making if their relationship with Industry is not at arm's length and transparent (Herxheimer, 2003).

Patient reported outcomes data, such as symptoms, satisfaction with care and treatment adherence is also gaining in importance in clinical trial design. Industry articles cite how there is an increasing focus on the patient perspective in decision making, particularly in conditions such as sexual dysfunction (Cappelleri and Stecher, 2008). In these circumstances prescribers and payers may benefit from subjective information to better define the value of drugs. Arpinelli and Bamfi (2006) acknowledged that if a positive impact on a patient's health status and daily life can be demonstrated, this additional data can differentiate a drug from its competitors aiding its diffudion and may enable a higher price to be achieved.

2.3.7. Marketing and promotion activities

Marketing and other forms of promotion exist to increase sales of products beyond the level that would occur if such activities did not take place. It is therefore a major driver of pharmaceutical diffusion. In their evidence to the HCHC Inquiry, GlaxoSmithKline explained how marketing is "entirely legitimate and neither the ABPI Code of Practice,

nor the Medicines Act, nor the EU Directive on the Advertising and Promotion of Medicines prohibits this activity" (HCHC, 2005).

Permissible marketing activities are set out in the ABPI Code of Practice and regulated by the Prescription Medicines Code of Practice Authority, which was established by the ABPI to operate independently of the Association. The MHRA also has a responsibility to rigorously monitor promotional activities examining practices and responding to complaints (MHRA, 2012).

The publicly available Code (ABPI, 2012b) is explicit about the term 'promotion' which includes:

- the provision of inducements to prescribe, supply, administer, buy or sell medicines, by the gift, offer or promise of any benefit or bonus whether in money or in kind;
- the provision of hospitality;
- the sponsorship of scientific and other meetings including payment of travel and accommodation expenses.

The concept of self-regulation however is a contentious one. Numerous incidents over the past few decades have brought pharmaceutical marketing practices under scrutiny and criticism, drawing into question the capacity of the Industry in the UK to undertake self-regulation. A study of marketing practices by Devlin *et al*. (2007) obtained through the HCHC Inquiry identified serious breaches of the Industry's own ABPI Code of Practice, concluding that "the regulatory framework in the UK appears insufficient to prevent systemic violations of prescription only medicine advertising". The Industry argues that self-regulation preserves government resources, that companies in

competition with each other are likely to be the most expert and sensitive critics of their competitors' behaviour and that penalties for transgression are substantial. They are also acutely aware that direct government control is less preferable.

Clinicians are also given clear guidance through the General Medical Council (GMC) guidelines of appropriate conduct when dealing with Industry, including the statement "You must not ask or accept any inducement, gift or hospitality which may be seen to affect your judgement" (GMC, 2008). This begs the counter-argument that clinicians have an equal responsibility to be accountable for their behaviour and practices as those being levelled at the Industry. There are numerous publications cataloguing the various ways in which pharmaceutical companies are claimed to influence clinicians. These range from the seemingly trivial (the subliminal messages conveyed through branded pens and note pads) to the support of lavish trips and entertainment (Moynihan, 2003). While not confined to the past, the era of generous inducements offered to clinicians as a means of altering their behaviour has become somewhat curtailed. This is likely to be a result of increasing scrutiny, but also by what appears to be a societal shift in the perception of the motivations of those people in positions of power who respond to these inducements. Registers, such as the Sunshine Act in the USA that came into force in April 2012 and which compulsorily requires companies to list payments to individual doctors, are likely to be inevitable in the UK (Cohen, 2011).

One purpose of marketing is to disseminate knowledge. The availability of a drug is of limited value unless prescribers are aware that it exists and has access to scientific and medical information to know how to use it effectively. The view presented by pharmaceutical companies is that they consider themselves to be the most knowledgeable source of information about new drugs and so have a role to play in

providing information to many stakeholder groups to ensure the appropriate use of medicines (Yager and Starrett, 2006; Niblack, 1997; Spiegel, 1991; Peretz, 1978). Views of prescribers are mixed in relation to this point. Studies with GPs have shown they are "largely reactive recipients rather than active searchers of new drug information" and therefore rely on the Industry as a convenient and accessible source of information (Prosser *et al*., 2003; Prosser and Walley, 2003a). Clinicians qualify this by indicating they usually need to seek further information or a colleague's opinion before prescribing. Others take the view that this information provision role should not be left to the sponsors of the drug who will inevitably present the findings within the context of a particular agenda, but this underplays a clinician's ability to recognise company sponsored information for what it is.

2.3.7.1. Promotion

Promotion is just one component of the 'marketing mix'; the other components being price, product and place. Marketing can therefore exist without promotion, but promotion does not exist independently of marketing. Within promotion, there are a further four elements that comprise the 'promotional mix' (advertising, personal selling, sales promotion and public relations). Industry authors have stated that information provision on their products is just as much a part of their role as research and development (Medd, 1983). Snell (1986) argued that any criticism of promotion therefore, should be confined to its quality and quantity, but not to its need. Promotion serves multiple functions; it provides prescribing information for clinicians and a means by which clinicians can feedback information about new products to the companies via representatives. Promotion and marketing spend accounts for approximately 15% of

sales revenue (Azoulay, 2002). Increased awareness of a drug can also stimulate product improvements by competitors.

Advertisements

In Europe, advertising is restricted to prescribers. The placement of adverts in medical journals, either for broad dissemination within high impact journals, or to select audiences in disease- or sector-specific publications provides a channel of communication to create awareness. However, in evidence to the HCHC (2005), the Industry implied that its impact is questionable. Despite promotion being regarded as intense, the reality is that the speed of uptake of new drugs in the UK is comparatively slow. Even when drugs receive positive NICE recommendations, some drugs are still not adopted, which members of the Industry believe counteracts the suggestion that the level of promotion is influencing things in any one direction. However, a question that could be asked is why would a company spend the vast sums of money on advertising if it was not impactful? It is difficult to measure the return on investment from advertising, as unlike the situation with medical representatives, it is not possible to determine the correlation between who is being exposed to the message and those prescribing the drug. Independent studies such as that by Jones *et al*., (1999) have not been able to demonstrate a clear relationship between the extent of advertising and the amount of prescribing, concluding that advertising is just one of many other influential factors.

Medical representatives

Medical representatives (also referred to as reps, detailers or field force) are considered by the Industry to be key in communicating information about drugs to health professionals as they offer the flexibility to tailor information to suit specific needs.

There are approximately 8,000 medical reps in the UK, with the ABPI Code of Practice stating that "the number of calls made on a doctor or other prescriber by a representative each year should not normally exceed three on average" (HCHC, 2005). Traditionally general practitioners have been the prime focus of detailing efforts, however as Gaedeke *et al*. (1999) noted, the number of individual prescribers accessible to representatives has been reducing through formation of clinician groups and restricted formularies which limit an individual physician's discretion in drug decisions. The Industry literature highlighted how over the last ten years, while specialist influence has remained constant, there has been a clear shift in influence from GPs to payers in the NHS and an increasing importance of key opinion leaders in decision making (McClearn and Croisier, 2011). The ability to adapt marketing strategies to reflect these changes can enhance the diffusion of a company's product, but as Ruzicic and Danner (2007) acknowledged, many companies have a cautious approach to dealing with changing healthcare environments, with some struggling to develop new business models to interact with their most influential customers. Occasionally co-promotion using the expertise of other companies is used to complement a company's own resources if they are marketing a new drug in an unfamiliar disease area.

As one of the most expensive aspects of marketing, it is clear that the Industry value the 'rep model'. While the Industry literature is reluctant to document the dynamics of the interpersonal relationships they forge with clinicians, there are many commentaries that have outlined the tactics companies are claimed to use to manipulate clinicians. They describe it as not simply an information exchange, but an attempt to influence through false friendships that are often not recognised as such (Fugh-Berman and Ahari, 2007). Some clinicians have stopped rep visits, instead encouraging other prescribers to use

unbiased sources of information in preference. With the increasing importance of prescribing formularies and monitoring of their implementation, the individual clinician model is likely to be limited in its influence.

Product samples

The provision of prescription medicine sample packs (starter packs) aims to attract new customers by allowing clinicians to develop first-hand experience with a drug through observing the effects in their own patient population. The Industry literature accepts that samples aid a drug's diffusion as once patients have started therapy with a particular drug and no significant side effects are apparent, they are unlikely to switch to alternative drugs (Kyle *et al*., 2008). While being candid with regard to this benefit, it could also be argued that supplying drug samples is an opportunity to gain face to face access to clinicians and habituate them to prescribing particular drugs (Fugh-Berman and Ahari, 2007).

Branding

The importance of brand names was identified in the Industry authored literature as a means of communicating differences between drugs in a class. They also serve as an identifier of quality and consistency in relation to a company's reputation, which they believe may play a role in prescribing decisions, and therefore has a bearing on diffusion (Hoare, 1974).

2.3.7.2. Continuing Medical Education (CME)

Over half of all clinician postgraduate education and training is funded by the Industry conducted in various partnerships with academia, health professionals and their

professional bodies and government (Leather and Davis, 2005). Medical education is considered separately from promotional activities on the basis that CME events are led by senior healthcare professionals to deal with issues related to clinical practice and are not forums to promote individually branded products (unless as the first of a new class) (Davis, 2004). Leather and Davis (2005) indicated that much of the finance for these events is provided unconditionally, with no control by Industry over the content or style of delivery. These events however, can enhance diffusion if prescribers need to be made aware of changes to clinical practice that may ultimately favour the use of a drug, or its class (Blake, 2001).

Boccuzzi (1999) used the example of angiotensin-converting enzyme (ACE) inhibitors to highlight that despite the existence of clinical guidelines and a large body of evidence, these agents were underutilised and inappropriately dosed. The Industry played an important role to increase adoption of this class through support for professional education and evidence-based practices. Rajfer (1993) similarly described how publication in high impact journals does not guarantee awareness amongst prescribers. Among physicians familiar with a heart failure trial published in the New England Journal of Medicine, less than half were able to identify the ACE inhibitor used in the study, which supports the Industry view that there is a need for targeted dissemination of information related to therapeutic advances.

Education not only extends to physicians. Companies produce medical education materials that are used as aids to discuss the risks and benefits of new drugs with patients. When risks are perceived by patients and clinicians to be significantly greater than indicated by scientific evaluation, it can have a direct and profound impact on

uptake and diffusion (as exemplified by cases such as the MMR vaccine (Leather and Davis, 2005)).

Views from those outside the Industry on their involvement with CME take a more critical stance, perceiving it as an extension of their marketing campaigns (Moynihan, 2008). Relman (2001), described how pharmaceutical companies have assumed a role in CME that is inappropriate for an industry with a vested interest in selling prescription drugs. He also criticises how medical institutions solicit Industry participation in activities that should be the sole responsibility of the medical profession. In a report for the Josiah Macy Foundation, Professor Suzanne Fletcher also declared how "no amount of strengthening of the firewall between commercial entities and the content and processes of continuing medical education can eliminate the potential for bias." (Fletcher, 2008). The question about the funding gap that would be created if the Industry were excluded from CME activities, emphasises the need for a cultural change in the way CME is delivered. There have been recommendations that the current model with its emphasis on lectures (learning what to do) moves towards focusing on a more practical approach of helping clinicians measure and improve what they do in their practices (Fletcher, 2008).

2.3.8 Safety/ Regulation

Safety concerns

Industry authors have been keen to highlight the limitations of the current system of regulatory approval, which requires testing in around 3,000 patients, with specific high risk or complicated populations invariably excluded. For a drug to receive marketing approval, all results in relation to the approved indication (positive or negative) are

provided to regulators, but it is only once a drug has been in use in the general population that many adverse events that were not detected during the manufacturer's pre-marketing clinical investigations start to emerge (Sullivan, 1990; Tilson, 1988). Safety concerns are detrimental to diffusion, but to varying degrees, ranging from a minor decline in usage to complete market withdrawal.

Sir Richard Sykes, the former chairman of GSK in 2006 stated that the best way to minimise risk is to "introduce novel drugs slowly and then watch for potential adverse events. If they occur you have the opportunity to understand them" (Sykes, 2006). This is somewhat counterintuitive to the Industry's role in accelerating adoption, but if an 'at risk' group can be identified and monitored or excluded, the Industry's view is that a drug has the potential to be considered safe in the majority and should not be withdrawn. When drugs are adopted too rapidly, often as a result of media coverage, this can jeopardise any chance of continued controlled diffusion. This sudden exposure of a large population can reveal high rates of adverse events, permanently tainting a drug and requiring its withdrawal. Personalised medicine is anticipated to reduce safety issues as it becomes easier to predetermine at risk individuals before a drug enters the market. Despite this, all drugs do carry risks and as Hartford (2006) outlined, it is important for safety decisions to be evidence-based rather than reactive.

Labelling

Yager and Starrett (2006) indicated in their commentary that "unfortunately there have been instances where physicians prescribed products incorrectly despite warnings and guidance from regulatory agencies". This can have a significant impact on the way the medicine is then subsequently perceived by patients and the public and detrimentally impact upon its diffusion. Arguably, the companies involved could make a more

concerted effort to address inappropriate use, but until a safety issue is raised this is seldom a key marketing message as there is the potential it may expand drug use.

According to Bush *et al.* (2005) “safe medicines refer to those drugs whose benefits have been found to outweigh their risks when they are used according to the approved labelling”. These authors and others have highlighted the importance of labelling as an education tool in ensuring that clinicians and patients are informed of the risks and benefits of a new drug and that any marketing claims have to be consistent with explicit statements in the labelling. The risks have to be clearly communicated as concerns about adverse reactions listed in the labelling may deter apprehensive patients from initiating drug therapy (Robinson, 1994).

Benefits and risks in the post-approval phase are evaluated through a reactive system of spontaneous reports and post-marketing surveillance studies (Bush *et al.*, 2005; Blake, 2001; Sullivan, 1990), but a more proactive stance is being required by regulators. The FDA for example, now requires companies to produce risk mitigation strategies, which has elevated the rigour with which manufacturers must fulfil post-marketing safety commitments (Nicholson *et al.*, 2012). These strategies may incorporate medication guides if regulators determine information related to possible side effects could influence a patient’s decision to initiate, or continue to use a drug, and communication plans for clinicians to assure the safe use and implementation of new drugs. Appropriate communication of not only the benefits, but also the risks is, according to Industry, an essential factor in pharmaceutical diffusion (Hartford, 2006).

Regulation

Several authors have responded to criticisms levelled at the Industry's close relationship with regulators, commenting that communication is an essential process throughout the entire lifecycle of a drug, not only in accelerating market access, but also managing safety issues efficiently to reduce the potential impact on diffusion (Heidenreich, 2006; Bush *et al*., 2005; Amery, 1994; Hartford, 2006). Industry authors described how the UK has a prominent voice in international regulatory matters through the reputation of the MHRA and the UK-based European Medicines Agency (EMA), which can ultimately influence the environment into which a drug diffuses (HCHC, 2005).

While it is accepted that the Industry has to operate effective working relationships with the regulators, there are concerns about the more covert influences, such as what has been referred to as the 'revolving door policy'. It is claimed that in the UK a large proportion of scientists working within the regulatory sector originally worked for Industry and many move back there. The concern is that this conflict could introduce values sympathetic to the pharmaceutical companies resulting in awarding them the benefit of scientific doubt when reviewing products (Abraham, 2002). There has also been an insidious culture around reducing times to approval, instilling competition between regulatory agencies. Abraham (2002) highlighted how the UK reports some of the fastest approval rates, which ultimately aligns with the interests of the Industry.

Regulators are often accused of using experts to review safety and efficacy data during the regulatory process that are not entirely independent of the Industry. This is not just a problem for regulators, but for all organisations that depend on expert input. The very nature of their expertise is a consequence of their involvement with a technology and

this ultimately leads to potential conflicts. Adoption of a pragmatic stance of transparency, whereby conflicts of interests are declared and managed appropriately, is necessary in these circumstances. In addition, there is criticism of the confidentiality agreements that exist between the regulators and the Industry, which restricts any other interested parties including medical and scientific communities having access to the data they hold. While there appears to be a changing attitude from the Industry due to pressure from the AllTrials campaign, they are reluctant to sign up to full public disclosure because of public concerns over preserving patient anonymity.

2.3.9. Competitors/Generics

Competitors (fast-followers)

While recognising the potential detriment of competitor entry, an Industry view provided by Yager and Starrett (2006) concluded that there is a place for fast-follower or 'me-too' products in that molecular refinements lead to improvements in the clinical utility of therapeutic classes. Spiegel (1991) also argued that the perception that a drug entering second or third in its class is "simply a copy quickly brought to market by a competitor as they observe the success of the first product approved is not supported by the realities of the 10-12 year process required for drug development". Decisions regarding R&D investment are made by companies when the arrival of future competitive agents is unknown. Simultaneous, often closely similar research efforts by several companies usually result from the rapid, global dissemination of scientific advances (Spiegel, 1991; Yager and Starrett, 2006). It is often a race to be first on the market and until the trials are done, and the drugs are approved, it is unclear which is going to be the 'new' drug and which will be the 'me-too'.

A criticism of the Industry is that they consistently fail to conduct head to head trials that are necessary to demonstrate the superiority of one drug above another in a class (Estellat and Ravaud, 2012). For drugs in simultaneous development, it is accepted that comparative trials cannot be conducted before the drugs are licensed, however late entrants to a class are often introduced with placebo rather than comparative study data. Comparison with placebo is all that is required for approval by the regulators, but this falls short of what is required by clinicians to aid decision making.

Generics

While a generic drug generally curtails the diffusion of its branded counterpart, it can also detrimentally impact on drugs within the same class still on patent. Iglehart (2003) and several other Industry authors have highlighted a scenario that while R&D time and expense has been increasing, the time to recoup R&D costs has been gradually reducing (Kramer, 2011; Berger and Grainger, 2010). Some generic companies no longer wait until patent expiry to enter the market, either through earlier patent challenge, or claims of non-infringement despite the presence of valid patents. The incentive to be the first generic is substantial as there is a period of several months of exclusive sales at 80-90% of the brand-name cost. Devoid of the need to invest in R&D, generic companies can afford to engage in litigation so as to not have to wait for patent expiry. Garnier, the CEO of GSK in 2003, presented the case of Paxil, which experienced generic challenge five years after market entry in what should have been a 14 year effective patent life (Iglehart, 2003). In the following three years, a further seven companies applied to market a generic.

Patent extensions through reformulations or combination products are often viewed as strategies to stave off the generic impact on diffusion; a term referred to as ‘evergreening’. They are often released just before patent expiry to encourage prescribers to switch ahead of generic introduction, on the basis that patients are unlikely to be switched back. In addition to extended release and combination products, an increasing number of patent extensions are focusing on use in children. The EU permits an additional six months of patent protection if efficacy can be demonstrated in this group as they are generally excluded from the initial regulatory trials. An Industry perspective provided by Marlow (1994) however, argued that these developments are genuine responses to clinical need.

Hoare (1974) presented a different Industry perspective on generics, commenting that the cost savings from generics are somewhat marginal, the impact only really being apparent on diffusion if, at patent expiry, the product is still widely prescribed (not having already been superseded by a branded competitor), and its market price has remained high throughout its lifecycle. The greater impact from a diffusion perspective is therefore posed by other branded competitor products. This view is however, unlikely to reflect the current situation where the price of some blockbuster drugs remains consistently high throughout their lifecycle.

2.3.10. Mass media

It could be perceived that the print media sometimes take a polarised stance on medicines. They have a tendency to portray them as either ‘killer drugs’ or ‘miracle

cures'. This may distort the public perception of the benefit/risk debate. When safety issues arise on commercialisation of a new drug, premature release of information ahead of completion of assessment by regulatory agencies or the company can, according to Industry commentators, have permanent consequences on diffusion. Yager and Starrett (2006) noted that complex scientific messages are often needed to counteract the negative 'sound bites' in the media, but this can create a communication barrier with the public, adversely influencing diffusion through a loss of confidence. While the media can be considered as an unsophisticated tool for conveyance of certain types of messages, the Industry do exploit this medium to bypass the direct to consumer advertising restrictions imposed in the UK by way of enabling them to bring disease awareness to the attention of a wide audience.

2.3.11. Government priorities

In a publicly funded health system, government departments are involved in nearly all aspects of drug development and market access. In the UK, they subsequently have significant influence on diffusion through NIHR organisations involved in research, through the regulatory system via the MHRA, through assessment agencies including the NIHR HTA programme and NICE, through to policy initiatives that either support a particular drug class or that focus attention on a particular disease, or alternatively places restrictions on access. Pharmaceutical companies recognise the importance of coupling innovations to key government priorities in ensuring successful uptake of new drugs and through PICTF it was agreed that there should be close joint working between Industry and Government on the National Service Frameworks that set standards for the NHS in clinical priority areas (HCHC, 2005).

However, as with the involvement of the Industry in professional education, some regard their involvement with the political system equally unsettling (Heath, 2011). Industry authors regard public policy engagement as a way of conveying their perspective on issues such as barriers to access, counterfeit drugs, illegal importation and challenges to intellectual property protection. Several articles have made assertions about the close relationships that members of the Industry have with guideline developers and those in academic institutions (Norris *et al*., 2012; Choudhry *et al*., 2002; Bekelman *et al*., 2003), but there is now a strong requirement to disclose financial conflicts of interest for authors and formal processes for discussing these conflicts prior to guidance development. Lobbying activities however, currently do not have to be registered, therefore there is no public record of the nature and extent of the Industry's interactions with politicians.

2.3.12. Supply

Supply issues, while not featuring prominently as a common diffusion factor, can have an impact on a drug's uptake. Drug manufacturers have a responsibility of aligning capacity with future anticipated demand to ensure the uninterrupted supply of safe pharmaceuticals (Van Arnum, 2011). However, additional supplies of drugs coming into the market, either through illegal counterfeit medicines or from the parallel import of branded drugs from countries outside the UK curtails the diffusion ceiling of a drug below expectations (Barr, 1994).

2.4. Case study specific diffusion factors

In a rare insight, Kvesic (2009), a marketing director at Bayer Healthcare Pharmaceuticals (USA), published an article detailing the key factors that were instrumental to the success of nifedipine (Adalat) at particular stages of the drug's lifecycle, and those that presented barriers.

Many of the factors were consistent with those highlighted in the Industry authored commentary material. There was support for the importance of meeting clinical need through reformulations to improve patient compliance. Through that need, new indications were developed (angina through to hypertension). While reformulations are often dismissed as a lifecycle extension strategy, 15 years of modifications to the molecule were necessary before nifedipine reached its optimum form and was suitable for the hypertension market. Contrary to popular belief, lifecycle extension strategies in this case did not result in keeping the price of the drug high. The improvement from a three daily dose (which had become generic) to a twice daily dose (patented) meant that the cost of the new formulation of nifedipine could be provided at 25% less than the daily generic cost. The article confirmed the importance of the perceived role of evidence, clinician education and opinion leadership support, but it did provide additional insights as to the impact a company's reputation based on its behaviour and approach to the market can have in terms of how it and its drug is received by the scientific community. The key events are outlined in Table 2.1.

Table 2.1: Key factors outlined by Kvesic (2009) in the diffusion of nifedipine (Adalat)

	Factor	Description
1.	Reformulation to improve dosing	*Angina indication* • Novel mechanism provided first in class position, an advantage that enabled market leadership. • Adalat name chosen for international translation and enabled the drug to appear first in guidelines and formularies. • Initial R&D strategy focussed on a variety of formulations to improve patient compliance. • Intracoronary and intraventricular line extensions experienced limited success as they were complicated to use. • Clinical need existed for a once-daily formulation to improve patient compliance, but initial attempts proved difficult. Developed a twice-daily formulation within 5 years. Bayer introduced a lower 10mg dose of the twice-daily formulation in some markets which proved very successful in the UK where authorities were more reluctant to approve higher doses.
2.	Indication expansion in a growing cardiovascular market with unmet need (shift from angina to hypertension was pivotal)	*Hypertension indication* • Guideline recommendations highlighted hypertension as a major risk factor for cardiovascular disease. Adalat was an effective agent for lowering blood pressure. • 10 years of modification to formulation required before molecule was suitable to expand into hypertension market. • Presence in the cardiovascular market with the angina indication helped sales force introduce the hypertension indication. Many patients have both conditions. • As hypertension is a chronic condition, it provided an opportunity for Adalat to build brand loyalty over time. • Product reached its optimum form 15 years after launch. The current environment requires a drug to be 'near perfect' before approval, allowing fewer opportunities for improvements and reformulations.
3.	Global uptake through staggered launch	• Bayer launched the once and twice daily formulations within a 2 year period. The staggered launch strategy increased the probability of success as best practices and tactics were shared from country to country. In the current global regulatory environment, this strategy is no longer possible.
4.	Maximising brand loyalty through Bayer and Adalat's heritage, scientific and promotional activity	• Pre-launch period spent promoting and positioning Bayer in CVD therapy area. Created awareness through international and national thought leader interactions, education and publications about the new class and molecule. • Success of creating drug class awareness hinged on support from American cardiologists who ran clinical trials and generated a publication in a high impact journal (NEJM). • Bayer supported the organisation of a key European Congress in cardiology which built scientific contacts and created brand awareness and credibility. • Thought leader network that supported Adalat throughout its lifecycle was key to presenting the safety data when under scrutiny.
5.	Licensing to capitalise on promotional opportunities	• Entered a licensing agreement with Pfizer to market in the USA - after 4 years licence would return to Bayer. When Pfizer developed a once daily formulation, Bayer was able to sub-licence the molecule outside of the USA.
6.	Pricing strategy through 'cannibalisation' of existing business	• Refocussed resources from the angina to the hypertension market. • Selected pricing models in countries where generics offered a 25% discount to the brand price, so that the twice daily branded molecule was priced at 75% of the generic three-times daily price. • In some markets the twice-daily formulation was removed to focus resource.
7.	Introduction of fixed-dose combinations (FDC)	• Limited success of FDC in the early part of the lifecycle due to lack of internal support. While current guidelines recommend the use of combination strategies to control hypertension, the initial reluctance of the company to revisit the strategy presented a competitive disadvantage and may have limited the potential of the brand.
8.	Clinical trials	• Second growth phase supported by series of scientific and clinical trials to strengthen the marketing messages. • Long-term intervention studies provided academic credibility and strengthened reputation of company. Cost had previously prohibited these studies. • Some trials were planned in response to safety issues raised by a meta-analysis (attributed the effects to the 3 times daily formulation, but as the formulation had improved, many physicians dismissed the claims). • Trials confirmed what physicians knew and had experienced with the drug previously.
9.	Other factors	• Withdrawal of Bayer's cerevastatin increased priority of Adalat and provided newly available field force in some markets. • Complex structure of the molecule made it difficult to reproduce, extending its exclusivity. • Strong brand loyalty contributed to by the trusted, non-aggressive reputation of the company. Avoidance of aggressive competitor–targeted activities and promoting scientific activities was well received by scientific community.

2.5. Empirical studies assessing Industry views

In addition to the direct contributions to the literature from Industry personnel, there have been several studies conducted across different research paradigms that have sought Industry views on a range of topics. To aid comparison of these empirical studies, summaries of those that have touched on diffusion issues are presented in Table 2.2.

While questionnaire-based study designs have been able to access larger numbers of Industry participants, the qualitative studies utilising methods of face to face interviewing (consistent with the design adopted for this research) have been much smaller in scale, including between 1 to 17 companies and 5 to 49 interviewees. These studies have demonstrated that the Industry is not unwilling to speak in a research capacity, although several studies have indicated in their methodology that they had intended to include more subjects than they were able to achieve. Response rates however, were rarely reported and very few of the empirical studies included examples of raw material to assess the reliability of the data.

Only three studies were conducted in the UK, with most being relevant to Australia and the USA health systems. Many studies did not name the companies who participated so it is difficult to determine parallels with companies operating in the UK. Most importantly, the nature of the research topics focussed on very specific issues, or topics that have concerned specific groups of Industry personnel, and none have used a case study approach to elicit the views of the Industry, which make it difficult to draw any conclusions with regard to holistic diffusion influences from these studies.

Table 2.2: Empirical studies that have ascertained Industry views on potential diffusion factors (n=25)

Study (Country)	Study aim	Method of study	No. companies/ respondents	Type of Respondent	Companies	Outcomes/results/findings
Marketing and Promotion						
Al-Areefi *et al*., 2012 (Yemen)	Exploration of medical representatives views on drug promotion techniques.	In-depth face to face interviews.	14 Co./ 14 respondents. (Response rate not specified)	Industry representatives.	Multinational and generic medicines companies.	Factors considered important in drug adoption included provision of free medical samples; use of educational materials; symposia and scientific meetings; gift and incentive provision and commercial offers. While respondents were altruistic towards patients they were conscious of unethical practices.
Kyle *et al*., 2008 (Australia)	Exploration of Industry opinions about the importance of prescription medical samples.	Semi-structured interviews.	3 Co. / 5 respondents. (3 companies invited, all accepted)	Not specified	Pharmaceutical Industry Associations.	Prescription samples encourage early uptake of new medicines and provide leverage for companies to influence drug choice. Participants indicated that samples, which are generally for newer, more expensive products were expected and demanded by doctors; aided brand switching; provide early access to new medicines; facilitated prescriber familiarity, promoted brand awareness and was an attractive strategy in chronic disease markets.
Sokol *et al*., 2008 (USA)	Pharmaceutical representative perceptions of marketing ethics.	Postal questionnaire survey.	25 respondents. (25 accepted out of 50 invited)	Pharmaceutical marketing representatives covering central Florida.	Not stated.	Representatives have a positive ethical view of their activities. The vast majority believed doctors were less knowledgeable than themselves regarding the marketed drug, indicating an educational role. Only 10% believed that meals and gifts were not acceptable practices, as they did not perceive them as influential in prescribing decisions.
Ruzicic and Danner, 2007 (Europe)	Industry perceptions of sales force effectiveness.	Interactive survey.	119 respondents. (236 participated. Reduced to 119 when revenue criteria applied)	Senior Industry executives with geographical responsibility for Europe.	Large and mid-sized companies (anonymous - 18% were UK participants).	Changes in stakeholder influence require adjustments to sales force size and structure. The growing importance of payers in decision making has resulted in fewer representatives being needed than when GPs held a more prominent role. Intensifying competition from generics, weak product pipelines and few product launches, regulatory constraints on sales and marketing were also indicated as negatively impacting in sales force activities.
Parker and Pettijohn, 2005 (USA)	Comparative analysis of attitudes held by pharmaceutical representatives and physicians.	Postal questionnaire survey.	1 Co./ 90 respondents. (90 respondents out of 250 invited)	Pharmaceutical representatives.	US-based pharmaceutical company (anonymous).	Representatives believe that drugs they promote are more likely to be prescribed, yet they and physicians agree that representatives have minimal impact on determining the proper drugs to prescribe, with physicians requiring more information than what is provided by companies. There was agreement that while some promotional items are acceptable (samples however, were considered by both groups to have minimal impact), more extravagant gifts were to be discouraged for fear of the appearance of impropriety.
O'Donnell *et al*., 2004 (Canada)	Self-perceived role of pharmaceutical representatives as marketers and/or educators.	Postal questionnaire survey.	5 Co./ 309 respondents. (309 respondents out of 606 invited)	Pharmaceutical representatives.	5 Canadian pharmaceutical companies (anonymous).	Representatives perceive their role as educational rather than marketing and that the information they provide is accurate. Two thirds indicated that while they felt doctors found the information useful, they believe doctors perceive their main goal is marketing. Most respondents felt a university-accredited educational programme would improve the quality of detailing.

Study (Country)	Study aim	Method of study	No. companies/ respondents	Type of Respondent	Companies	Outcomes/results/findings
Smith,2003a; Smith, 2003c (UK)	Exploration of marketing quality in medical markets (pharmaceutical, medical device and diagnostic companies).	Semi-structured interviews.	8 pharma Co./ 20 respondents. (Response rate not specified)	Managing directors, marketing and sales managers.	UK companies (anonymous); 5 of the 8 described as 'first rank'.	Marketing strategy of many medical companies is weak, particularly in respect of target market definition. Survival is dependent upon competitors having even weaker strategies. A subsequent follow-up paper sought to explain these findings concluding that generic approaches to marketing strategy fails most companies, and that a tailored process is required.
Gaedeke *et al*., 1999 (USA)	Exploration of whether pharmaceutical sales representatives' perceptions regarding the value of services they provide are similar to those of physicians.	Questionnaire surveys.	67 respondents. (Response rate not specified)	Pharmaceutical sales representatives (PSRs).	Anonymous.	Both PSRs and physicians considered free product samples, detailing new products, promotional dinners and provision of research studies to be valuable services. PSRs were more neutral about the value of sponsored lunches and detailing old products. PSRs considered serving as expert consultants on new drugs and their role in recruiting physicians to post-marketing studies as valuable, a view not supported by physicians.
R&D						
Milne and Zuckerman, 2011 (USA) Zuckerman and Milne, 2012 (USA)	Exploration of Industry views on the business prospects for personalised medicine. Extension study.	Telephone interviews.	13Co./ 20 respondents. (Response rate not specified) 21 Co. (Response rate not specified)	Scientific and business personnel. As above.	5 biotechnology firms; 8 large pharmaceutical Co. 9 biotechnology firms; 12 large pharmaceutical Co.	Knowledge barriers particularly with regard to radically new medical areas (e.g. genetics-based personalised medicine) can be a significant barrier to adoption for innovations utilising this knowledge as it impedes communications of technology benefits. Despite these knowledge barriers, targeted drugs are more likely to become adopted as they tip the benefit-risk decisions in favour of approval as well as influence payers' product value assessment more favourably towards reimbursement.
Bianchi *et al*., 2011 (Italy)	Exploration of views on open-innovation from the Industry.	Interviews.	13 Co./ 20 respondents. (13 Co.accepted out of 20 invited)	CEOs, business development managers and trade associations representatives.	Amgen; GSK; Roche; Siena Biotech; MolMed; NicOx; Toscana Life Sciences; Newron; Gentium; Bioxell; Axxam.	Companies acknowledged they should use external ideas that originate outside the company as well as those from within for successful innovation. Research indicated that firms have gradually modified their innovation networks by including more external partners.
Bruni and Verona, 2009 (USA and Europe)	Industry views on dynamic marketing capabilities.	In-depth, semi-structured interviews.	6 Co./ 31 respondents. (Response rate not specified)	Senior managers in product innovation.	2 USA and 2 European global R&D-oriented companies; 2 local European companies.	Respondents indicated earlier involvement of marketing and sales departments in the innovation process could enhance decisions relating to which technologies to pursue, and provide practical input into clinical trial design regarding future positioning of the drug and prescribing physician characteristics.
Lane and Probert, 2007 (UK)	Exploration of Industry views of external knowledge sourcing versus in-house discovery.	In-depth interviews.	9 Co./ 13 respondents. (Response rate not specified)	High-level corporate executives within or close to R&D function.	Amgen; Biogen; BMS; Genzyme; Johnson & Johnson; Lilly; Merck; Pfizer; Wyeth.	Some companies in-license compounds regardless of whether there exists any in-house expertise or commercial presence in the company as long as they perceived the molecule has potential. Various strategies are used to identify and obtain externally developed compounds. Some companies use dedicated departments to systematically identify in-licensing candidates, while others take an opportunistic approach.
Safety and Regulation						
Berndt *et al*., 2005	Improving communication between Industry and regulators (FDA).	In-depth-Interviews.	17 Co./ 49 respondents.	Senior level R&D or regulatory personnel.	7 biotech companies; 7 pharmaceutical companies; 3 contract	Industry seeks additional formal and informal interactions with regulators, particularly during phase II trials to assist in protocol reviews and decision making to reduce clinical development time. The authors

Study (Country)	Study aim	Method of study	No. companies/ respondents	Type of Respondent	Companies	Outcomes/results/findings
(USA)			(Response rate not specified)		research organisations (anonymous).	suggest involving Industry in regulatory oversight boards and creating accessible regulatory knowledge databases containing safety information on previously developed/failed drugs to reduce unnecessary uncertainty and delays due to lack of communication and interaction.
Medical research						
Blum *et al*., 1986 (Switzerland)	Exploration of differing attitudes of Industry and academia towards controlled clinical trials (CCTs).	Consensus conference focus group.	23 Industry respondents. (Response rate not specified)	Not stated.	Large sales volume pharmaceutical companies.	Industry considered regulatory requirements were too complicated and that complex registration requirements and inadequate patent protection inhibited new drug development. Industry agreed with academics that a proliferation of 'me-toos' could inhibit CCTs where needed, and mostly accepted that CCTs are difficult to justify if they do not improve medical practice.
HTA						
Assiff *et al*., 1999 (Canada)	Assessing Industry views on effectiveness of pharmacoeconomics (PE) departments, how they have evolved and future implications for PE.	Mixed: Face to face /telephone/ mail questionnaire surveys.	17 Co./ 17 respondents. (17 Co. accepted out of 21 invited)	Health economic personnel and CEOs.	Merck; Glaxo Wellcome; Astra Pharma; Janssen Ortho; Bristol-Myers Squibb; Pfizer; Abbott; Wyeth Ayers; Hoffmann-La Roche; Eli Lilly; Zeneca: Pharmacia & Upjohn; Searle Novartis; Hoechst Marion Roussel; Bayer; SmithKline Beecham.	Respondents indicated they perceive that PE work is valuable to the company. CEOs felt the true value of PE data is not adequately understood by formulary reviewers and therefore may be an impediment to market access. Industry has difficulties justifying the importance of PE assessment because of inconsistencies in the interpretation of economic evaluations by healthcare assessors.
Olson *et al*., 2003 (USA)	Industry perceptions of presenting PE models to Managed Care Organisations (MCO).	Telephone questionnaire survey.	10 Co./ 20 respondents. (20 respondents accepted out of 23 invited)	Directors; managers; medical liaison.	Various US pharmaceutical and biotechnology companies.	PE models optimise formulary positioning of drugs. Simple spread sheet models and well-designed regression models were the most effective for communicating this form of data to decision makers. Producing scientifically robust models, involving non-biased contributors; customising, simplifying and increasing model transparency (assumptions and calculations) were all factors identified as improving the use of these models, enhanced by presenter credibility and training that are key to gaining the respect of decision makers.
Armstrong *et al*., 2001 (USA)	Industry representatives' beliefs on important factors in drug benefit decisions of MCOs, with specific reference to health outcome and PE information.	Semi-structured telephone questionnaire interviews.	15 Co./ 21 respondents. (21 respondents accepted out of 47 invited)	Individuals involved in direct marketing activities.	Not stated.	PE information was not considered to be the most important factor in drug coverage decisions, ranking second to efficacy and safety. Use of PE data was related to the sophistication of the MCO. Adopter barriers included lack of expertise, no long-term focus and drug silo budgeting. Some respondents acknowledged PE information did not always meet customer needs and that they could be easier to understand.
Mass media						
Ulrich *et al*., 2010 (Switzerland)	Exploration of the role of media in improving company public image. (Industry interviews were	Explorative in-depth interviews.	1 Co. 8 respondents. (Response rate not specified)	Senior management team members.	Pfizer.	Public image of a company is important as it impacts on clinician perception, and can affect share price which ultimately impacts on R&D investment. Until recently the focus on physicians was too narrow, with the population and media not yet effectively treated as primary stakeholders. Patients are part of the 'public' and hence the population to

Study (Country)	Study aim	Method of study	No. companies/ respondents	Type of Respondent	Companies	Outcomes/results/findings
	part of a larger study assessing population views).					which indirect access is possible via the media. Pfizer needed to know which media were considered trustworthy by the population regarding health to improve its public image.
Van Trigt *et al*., 1995 (Netherlands)	Exploration of the role of the lay press as a communication channel for pharmaceutical companies.	In-depth face to face interviews.	7 Co./ 7 respondents. (7 Co. accepted out of 10 invited)	Public relations officers.	Sample from the top 10 companies in the Netherlands.	Mass media plays an important role in information diffusion, particularly around launch, or earlier if a disease is under-diagnosed. Its content however, is under the control of journalists who decide what becomes news and the manner in which it is presented and interpreted. Industry does not communicate early 'breakthroughs' to avoid creating false hopes, but this information is independently sourced by journalists from the literature. Safety issues are only communicated through the press when patients have to receive warnings quickly.
Opinion leaders						
Smith, 2009 (Europe)	Exploration of key opinion leadership (KOL) management strategies among European pharmaceutical companies.	Questionnaire and focus group.	18 respondents. (Response rate not specified)	Executives with KOL management responsibility.	European-based global pharmaceutical companies.	Companies are experiencing increasing difficulty with KOL management as networks of influence become more complex and there is greater competition for KOL support. Companies need to adapt their current approaches to integrate KOL management with other internal processes.
Cost						
Chaudhry and Dacin, 1997 (USA and Europe)	Exploration of business issues facing the Industry and response strategies.	In-depth face to face interviews.	10 Co./ 10 respondents. (10 Co accepted. out of 34 invited)	Pharmaceutical managers.	Bayer; Boehringer-Ingelheim; Bristol-Myers Squibb; Ciba-Geigy; Eli Lilly; Glaxo-Wellcome; Hoffman-LaRoche; Pfizer; Sandoz and Zeneca.	Industry reactively adapts the way it operates to accommodate regulatory controls. Priorities included i) reducing costs by optimal logistics, economies in scale of production and seeking R&D synergies with other firms; ii) distribution strategies; iii) forecasting negative impacts on demand (price-cutting trends, reduced clinician drug budgets, promoting health care economics); iv) developing new pricing strategies, v) reducing the impact of parallel trade. Industry indicated the need for effective lobbying of regulatory and government agencies to positively influence the business environment.
Government						
Wang *et al*., 2011 (Australia)	Eliciting views of Industry employees regarding collaboration with government initiatives.	In-depth, semi-structured interviews.	11 Co./ 24 respondents. (Response rate not specified)	Medical and regulatory affairs personnel.	6 innovative multinational companies; 4 generic and 1 non-prescription company.	Respondents claim a commitment to collaboration with government initiatives. Acceptance is underpinned by corporate or personal identification with the aims of the strategy, altruism with regard to improving individual and public health and increased Industry credibility. Resistance comes from divisions within company departments, either through lack of understanding or conflicting commercial priorities, or ambivalence (some respondents may be motivated more by external rewards and/or punishments than by an intrinsic commitment).
Patient groups						
Buttle and Boldrini, 2001 (UK)	Exploration of Industry relationships with patient advocacy groups.	Semi-structured face-to-face interviews.	2 Co./ 17 respondents. (Response rate not specified)	Product, brand and business managers; Senior executives.	1 UK-based pharmaceutical company (anonymous) and GSK.	Exchange of information through this conduit provides the Industry with a means of communicating with patients and other stakeholders which also encourages patient compliance. Additionally these relationships provide Industry with patient-sourced knowledge about the conditions.

2.6. Chapter comment

The literature review has gathered together a discrete set of factors, but the Industry has not been asked in a comprehensive way what they think are the drivers and barriers of diffusion, how these factors interact, how they as manufacturers respond to them, and then compare the outcome against other sources of diffusion data representing the same phenomena. The presence of Industry authors in the literature, albeit not to the same extent as any other stakeholder, indicates their desire to present their perspective. Most Industry contributions to the academic literature so far have been from non-UK sources, and while pharmaceutical companies operate globally, this research aims to provide an insight into specific perspectives from personnel in relation to the UK environment. Together with other factors derived from the wider diffusion literature, these broad themes were used to inform both the case study selection exercise of the research methods and provide the broad topic areas to explore further in the interviews with the Industry.

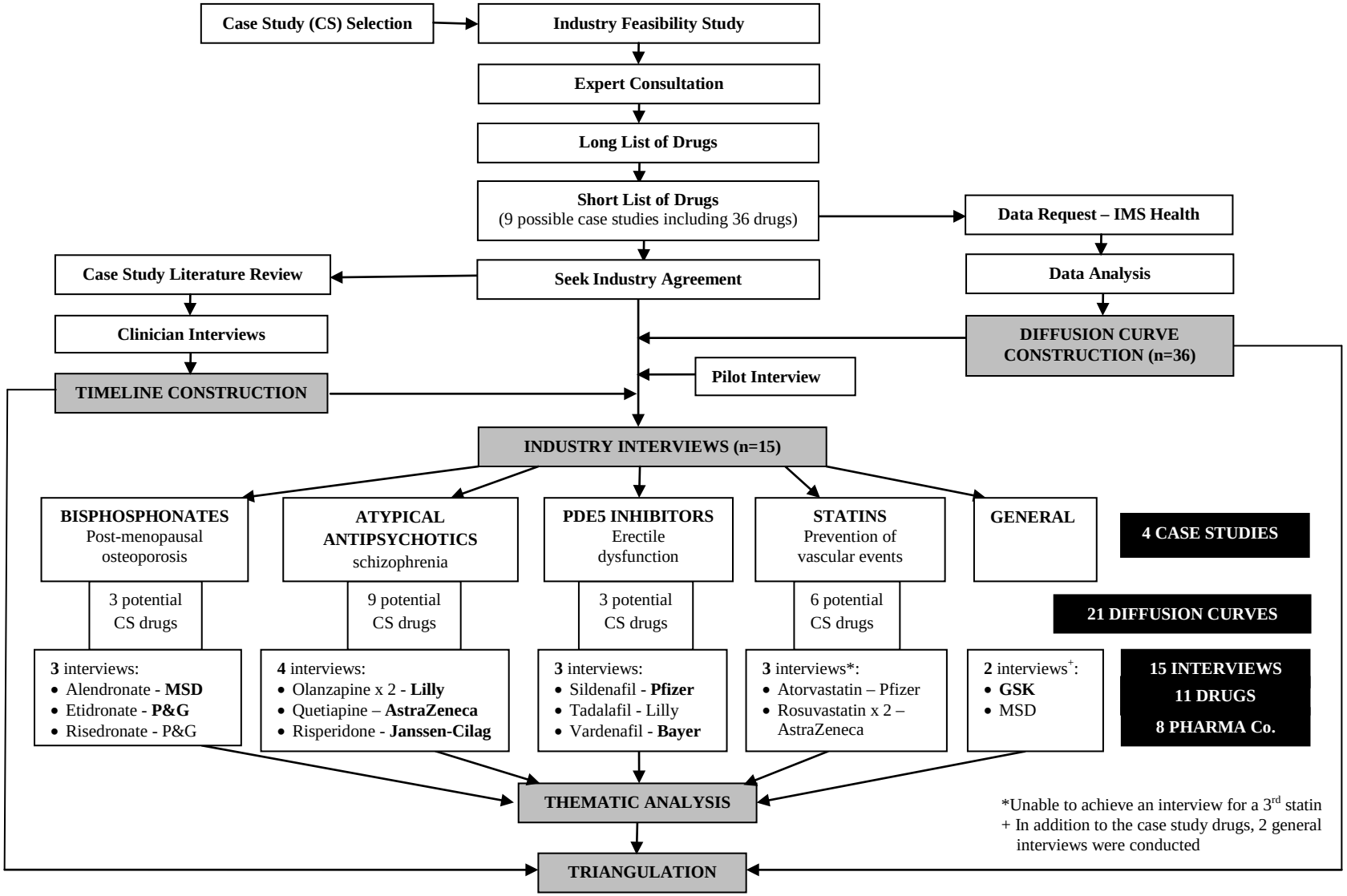
CHAPTER 3

METHODS

3.1. Introduction

This chapter outlines the multiple methods employed in this research to determine the views of the Industry on factors that influence the diffusion of pharmaceuticals. It begins with a justification for the use of case studies to explore the research question and the systematic approach with which the case studies were selected. In-depth, semi-structured interviews were the main method of data collection. A comprehensive description of the qualitative methods used to access and interview Industry personnel is therefore provided. Methods to construct the literature-based timelines and the quantitative methods employed to generate the diffusion curves used in triangulation are also described. A summary of the study design is provided in Figure 3.1.

Figure 3.1: Study Design Summary



3.2. Case study selection

3.2.1. Choice of case study methods

Competing positions in case study research

Case study research is particularly useful for examining phenomena in their natural context, recognising the complexities of the real-life setting and integrating multiple sources of evidence. There are two broadly competing positions in case study research, exemplified by Robert Yin (1994) and Robert Stake (1995), around which other commentators can be accommodated. Each position differs in its underlying philosophy. Yin is sympathetic to positivism and Stake to constructivism, and these sympathies infuse their methodological preferences. While each has a preference, they are also alive to claims of rival perspectives and therefore it is important not to overstate these preferences.

In qualitative research the case study method should be commensurate with the philosophical underpinnings of the inquiry as this enables the reader to judge how findings have been interpreted. A positivist approach is consistent with a realist ontology, which regards reality as something that is out there waiting to be discovered and epistemologically, we are external to the knowledge we are uncovering. Conversely, a constructivist approach (sometimes referred to as interpretivism) is consistent with a relativist ontology in which reality is constructed subjectively by people and groups, creating a series of competing accounts. Taking a relativist perspective therefore, accepts that other perspectives are equally legitimate, even if you as the researcher do not agree with the views of those being researched. In this paradigm, knowledge is not discovered but is interactively constructed and only comes to light through individual interpretation, thereby making the researcher part of that knowledge being uncovered.

The differences between the approaches of Yin and Stake to case study design have been well characterised in the critique by Appleton (2002) that outlined the following points of comparison:

Definition of a case – Yin describes a case as "an empirical inquiry that investigates a contemporary phenomenon within is real-life context, especially when the boundaries between phenomena and context are not clearly evident". Stake regards a case as an object and not a process, being "a specific, complex and functioning thing, with a boundary and functioning parts". The boundaries are kept in focus. What is happening and deemed important within those boundaries (the emic perspective) is considered vital and usually determines what the study is about, as contrasted with other studies where hypotheses or issues previously targeted by the investigators (the etic perspective) usually determine the content of the study. The case study according to Stake uses idiosyncratic instances to create understanding of more general matters (using exceptions to prove the rule).

Type of case study – Yin states that case study research can focus on either a single case or on multiple cases. These can be further defined as descriptive (documents a full description of the phenomenon within its context), exploratory (determines the feasibility of a study or defines questions and hypotheses of a subsequent study), or explanatory (demonstrates causal relationships). Stake suggests it may not always be possible to categorise case studies, but does describe three types: intrinsic (seeks clarity and understanding about a unique case); instrumental (a particular case is examined to provide insight into an issue or refinement of theory i.e. the case is not the primary focus); or collective (essentially an instrumental case expanded to incorporate a larger number of cases).

Paradigmatic orientation – The most obvious distinction between the two positions is that they have different paradigmatic starting points. Although Yin advocates qualitative and quantitative methods, his approach to case study research is considered by some to be essentially quantitative in nature (Stake, 1995). It follows a scientific framework to develop hypotheses, produce protocols to guide the investigation, collect empirical data and develop conclusions based on analysis of the data and therefore it could be argued that it is more consistent with a positivist viewpoint. Stake in contrast is influenced by a constructivist epistemology where knowledge is believed to be constructed and not discovered. It therefore requires purely qualitative approaches to uncover these multiple views about the case. Study designs emerge as the researcher interacts with study participants and begins to get a feel for important issues. While it is appropriate for a constructivist study to have clearly defined objectives and initial plans for preliminary data collection, Stake emphasises that these plans are often more tentative in nature. Commensurate with constructivism is the view that research cannot therefore be value free and is impacted upon by the researcher's own philosophical viewpoints. The co-production of truth does imply that the researcher is an active participant and that their views will inform the exercise, either through the selection of the topic itself, the theoretical orientation of the specific research questions, or the micro-sociology of interactions with interviewees.

Quality criteria – Consistent with Yin's positivist perspective, he recommends using criteria more commonly associated with quantitative studies to assess the quality of a case study, such as internal and external validity and reliability. Clearly any definition of internal validity which includes measures of internal consistency of groups of variables in scales would be inappropriate in constructivist work, which seeks to explore divergent understandings of a phenomenon. In terms of external validity, Yin

does acknowledge that statistical generalisability is inappropriate, suggesting instead that the researcher seek analytical generalisation. This involves an attempt to "generalise a set of results to some broader theory" and then use this "as a template against which to compare empirical results" (Yin, 1994). In doing so, this approach focuses on the etic perspective (outsider or objective – description of a behaviour or a belief by an observer). Stake's view of case studies is to deal with particularisation, focussing on the uniqueness of situations i.e. the emic perspective (insider or subjective – comes from a person within a culture) and not generalisation. Case reports can then help readers in their own construction of knowledge through vicarious experiences and not generalising findings to an existing theory. The responsibility lies with those who seek to apply or 'transfer' the study findings to other settings. These become naturalistic generalisations in which results become meaningful in terms of the reader's own experiences, derived from the tacit knowledge of how things are, why they are, how people feel about them, and how these things relate to other circumstances with which that person is familiar (Stake, 1995).

Sampling approach – Yin states cases should be selected at the beginning of a study to either "predict similar results (literal replication), or produce contrasting results but for predictable reasons (theoretical replication)". Stake's constructivist approach would not advocate explicit assumptions at the outset, but would be influenced by the realities encountered as the study developed. A case is initially selected due to its relevance to the phenomenon under investigation. The researcher then attempts to seek out the complexities of the case to provide greater insight into the issue of interest, often using purposive sampling to gather information rich cases.

Use of theory - Yin states that theory is helpful in designing a case study, but also later becomes the vehicle for generalising a case study's results. Stake however, avoids any

prior commitment to theory, taking the view it is impossible to adopt a theoretical framework at the beginning of the study as not enough can be known about constructed realities which may exist in the context under investigation. This perspective takes the view that no *a priori* theory could possibly encompass the multiple realities that are likely to be encountered, believing that if this were the case there would be no need to do the research. Stake regards theory as emergent, but his approach to case study emphasises the uniqueness and particularisation of the case and does not insist on theory development.

Despite oppositional framing of Yin and Stake by later commentators, it is important not to overstate the differences between them as there are inherent tensions associated with doing so, as outlined in Table 3.1.

Table 3.1: Associated tensions of oppositional framing of Yin and Stake in case study research

Case study elements	Yin (1994)	Stake (1995)	Tensions - commentary
Ontology	Realism.	Relativism.	-
Epistemology	Positivism (experimental) – there is an ultimate reality which the research is attempting to discover.	Constructivism – each individual constructs his/her own reality resulting in multiple interpretations. Knowledge is constructed rather than discovered.	-
Perspective	Objective An observer is providing a description of a participant's beliefs.	Subjective Participant and researcher are interacting to create knowledge together.	Yin's objectivist view is compromised by the fact the researcher does not simply reproduce participants' meanings. It is inevitable that a process of selection and interpretation informed by the researcher's theoretical framework intervenes between the researcher's observation and the account which they give of that observation (Murphy *et al*., 1998). Researchers have to interpret others' meanings and use strategies to avoid anecdotalism and the imposition of their prior assumptions upon the observations.
	Etic constructs are accounts, descriptions, and analyses that use as its starting point theories, hypothesis, perspectives, and concepts from outside of the setting being studied (imposition of prior theory). It allows for comparison across contexts and populations, and the development of more general cross-cultural concepts.	Emic constructs are accounts, descriptions, and analyses expressed in terms of categories regarded as meaningful by members of the culture whose beliefs and behaviours are being studied. There is a focus on the particularity of the context, in its respect for local viewpoints, and its potential to uncover unexpected findings.	In taking an emic approach, a researcher tries to put aside prior theories and assumptions in order to let the participants and data 'speak' to them and to allow themes, patterns, and concepts to emerge. This approach is often used when researching topics that have not yet been heavily theorised. In taking an etic approach, a researcher takes an existing theory or conceptual framework and conducts research to see if it applies to a new setting or population. Researchers have to navigate the tensions between these two extremes. Stake's approach advocates no prior assumptions impacting on interpretations, but since all researchers come with previous ideas, perspectives and commitments it may be impossible to be purely emic. Equally there is no recognition by Yin of the importance of tacit knowledge and intuitive processes in data collection. A completely etic approach risks blinding to potentially new and groundbreaking concepts.
	Questions are considered before embarking on the research and are of interest due to existing theory, previous research or own informed experience (hypothesis or issues previously targeted by the investigator determines the content of the study).	Questions emerge from within the data during the research process (what is happening and deemed important within those boundaries is considered vital).	
	Theory development takes place before data collection.	Impossible to adopt a theoretical framework at the beginning of the study. Phenomenon of interest must be discovered with flexibility to respond	

Case study elements	Yin (1994)	Stake (1995)	Tensions - commentary
		through progressive focussing.	
	Explanatory (laws) – deductive Hypothesis-driven/ confirmatory.	Exploratory – inductive.	Neither approach can be totally devoid of overlap between inductive and deductive approaches.
	Case study attends more to the pervasive (i.e. proving the rule).	Case study attends more to the idiosyncratic (exceptions) to create understanding of more general matters.	Yin's perspective is to use the case to test assumptions and so the emphasis on generalisation is stronger. Stake uses case studies to see where the general explanations fall down. Both however do this through an awareness of disconfirming evidence.
Focus	Not bounded – outside influences determine the content of the study. Series of case studies to test emerging theory.	Bounded – only concerned with the specific content of the case study. Focus in an intensive and in-depth fashion on one issue – on understanding the case itself.	-
Sampling	Theoretical or literal replication. - more emphasis placed on the method and the techniques.	Purposive - to give rise to interesting case studies. - crucial to case study research is not the methods of investigation but that the object of study is a case.	Probability sampling is not the intention of either approach.
Generalisability	Generalisable to theoretical propositions and not to populations or universes.	Naturalistic generalisation. Responsibility lies with the reader to relate findings to their own experiences.	While Yin's method comes from an experimental tradition, there is an emphasis on the need to be cautious about generalising. Stake approaches it from the other direction in that while his approach in no way constitutes an experiment, it is possible to generalise beyond the case study margins.
Methodology	Advocates using both qualitative and quantitative approaches.	Qualitative only.	-
Triangulation	Test of reliability – using multiple sources of data around the same phenomena to uncover an ultimate truth.	Test of validity – using multiple sources of data around the same phenomena to construct a richer picture (each providing supplementary information).	The tension arises here if one takes up a stable epistemological position on the nature of truth. Some researchers will make claims in relation to reliability and validity that are formally incoherent.

Influences on my choice of case study method

This research was an exploratory analysis of pharmaceutical industry views and was therefore suited to the methods of qualitative analysis. Neither Stake's nor Yin's approach to case study research however, was a perfect fit for this research. The approach taken was largely iterative and more constructivist in nature, but it is important to note that it did draw on pre-existing diffusion work as a starting point.

Paradigmatic orientation – Case study was selected as the research intended to undertake a detailed examination of a contemporary issue (pharmaceutical industry personnel views on diffusion influences) within a real life setting (the context of the pharmaceutical industry) using multiple sources of data to elicit a greater understanding about the case. The aim of this research was not to set out to test hypotheses, but to uncover a set of constructed realities from members of the pharmaceutical industry about factors they believed influenced the diffusion of the case study drugs. I used the available understandings from Industry respondents to inform my analysis, and from these I developed my analysis to build a more nuanced and subtle understanding, while remaining close to the original data. This is consistent with Stake's perspective, however, I did not start with a blank slate and these available understandings (from the literature and interviewees) have informed my analysis. For me this is more true to life that the position expounded by Stake, which implies that the analyst constructs understanding in a vacuum from first principles. The over-emphasis on construction, which ignores current understanding from which individuals build their understandings, is in my opinion a key weakness in Stake's position.

Definition of a case – While each individual case study in this research is concerned with the particular issues within its boundaries i.e. the emic perspective (exposing the

voice of the Industry respondents), the purpose of using multiple case studies was to use the information uncovered to provide a broader insight into diffusion issues, which is a heavily theorised topic (albeit from a particular perspective). While this is consistent with Stake's definition of a 'collective case study' where case studies are used to explore a wider issue beyond the case itself, generalising beyond the boundaries of a particular case study aligns more with an etic perspective.

Type of case – This study is examining Industry views across four different classes of drugs to increase the understanding about the phenomenon of interest i.e. pharmaceutical diffusion from a particular unique perspective. Therefore a collective case study exploratory in nature is being undertaken, as opposed to Yin's explanatory approach to uncover an ultimate account as to how and why the drug classes diffused.

Sampling – The approach taken to sampling was more consistent with Stake's constructivist position. Information rich cases were sought as opposed to cases that would test a particular hypothesis through a set of theoretical contrasts.

Rationale – Unlike Stakes' approach, which focuses purely on qualitative methods, both quantitative and qualitative methods were used in the case study research, which is consistent with Yin's perspective. The quantitative component was provided by the diffusion curves based on prescribing data of the case study pharmaceuticals. The qualitative component was represented by the interviews conducted with the pharmaceutical industry. The timeline information based on the literature and expert views provided additional contextual information, which enriches the interview respondent narratives.

Use of theory – Pure constructivism holds the view that it is impossible to use any theoretical framework at the beginning of a study as not enough can be known about the constructed realities that may exist. This perspective does not then sit comfortably with the idea of using Framework analysis, which uses an inductive refinement of pre-existing analytical categories. As mentioned previously, the concept of not having any *a priori* knowledge on a subject that you are researching, in practical terms is perhaps not a realistic perspective. Even when a largely inductive approach is taken, prior knowledge will have some influence in forming the analytical categories. I was therefore seeking to develop theoretical insights from new data, but being mindful of the existence of prior diffusion theory.

It is clear that there are inherent tensions that exist by adhering purely to one or the other of these two positions. Instead a pragmatic approach was taken to the research that adopted a largely constructivist position, but used aspects of Yin's perspective on case study methodology.

3.2.2. Industry feasibility study

Due to the sensitive nature of interaction with the pharmaceutical industry, a feasibility study was conducted at the outset (during April and May 2004) to determine whether the pharmaceutical industry would engage with the research. As the case study drugs were unknown at this stage, eight pharmaceutical companies selected from the ABPI's list of the top 20 UK pharmaceutical corporations in 2002 (predominantly major companies, but also some smaller firms with whom the NIHR HSC had established relationships) were consulted to determine the propensity for Industry participation in the study. Initial contact was made by email using NIHR HSC contacts initially, but

also involved personnel from the companies' marketing departments if referred by the contact. Companies were also asked whether they could provide quantitative data relating to marketing and whether they would discuss the specifics of marketing campaigns.

Initial discussions revealed that while there was a generally positive response from Industry to the concept (from seven of the eight companies contacted), it was evident there would be caveats around access and confidentiality (see Appendix 2). This highlighted the need for a pool of case studies from which a final selection could be obtained to compensate for potential redundancy of responses. Discussion of specific drugs was acceptable providing they were reaching the end of their product lifecycles, but the provision of complementary quantitative data was regarded as problematic. Other researchers have experienced similar issues of access to quantitative Industry data or printed materials, resulting in them having to rely solely on interview data (Smith, 2003a).

3.2.3. Expert case study selection exercise

A peer-review process with a selection of health care experts in medicines management was used to select cases based on interest (purposeful sampling frame), setting out the criteria for selection based on factors identified through the literature review and wider diffusion literature (see Appendix 3). Individuals were identified according to their experience within their respective fields, which included local and national prescribing committees (UK Medicines Information (UKMi) and the National Prescribing Centre), NICE, pharmaceutical advisors, representatives from the pharmaceutical industry, the ABPI, independent medical journalists, academia and public health.

Experts were contacted in December 2003 with the request to assist in the task of case study selection. A 10 year time frame (1990-2000) was applied during which the case study drug had to be launched based on the following general considerations:

- Data sensitivity – launch sufficiently far back so as to remove issues of sensitivity regarding marketing practices;
- Memory recall – launch not too far back as to compromise participant memory recall, particularly in an industry with high personnel turnover;
- Sufficient data – The year 2000 was considered the latest feasible year of launch considering the drug would need to have been on the market long enough for sufficient data to be available on its uptake and diffusion.

What were the experts asked?

Members of the expert group were asked to provide suggestions for interesting case studies guided by a typology of criteria of diffusion factors identified from the literature review and the wider literature on pharmaceutical diffusion. These included such factors as cost, evidence base and side effect profile of the new drug, service reorganisation issues, marketing and journal, media or patient group interest (see Appendix 3). Experts were asked to suggest up to 10 drugs with a brief explanation as to the reason for their choices.

The only other selection criterion applied was that the drugs were intended for use in primary or secondary care and not over the counter preparations. It was suggested that the selection did not only need to include 'blockbuster' drugs or those reviewed by NICE, and that individual drugs or classes of drugs could be nominated. Case studies

that had already been the subject of diffusion research were highlighted to avoid duplicating these examples.

Expert Response – Long list of case study drugs

Of the 14 experts contacted, 11 provided responses, which were collated and analysed in February 2004. Many of the suggestions involved classes of drugs, which brought the total number of suggestions in excess of 60 drugs. There was considerable similarity in the selection of drugs between experts, and many (over half) of those selected were ones that had already received NICE guidance or guidance was pending.

Short list of case study drugs

Nine drug classes (incorporating 36 drugs), representing a potential pool of case studies, were selected from the expert sample based on frequency of suggestion (i.e. at least four suggestions of the same class were necessary to qualify, the cut-off of four providing a basis on which to obtain a reasonable size pool) (see Table 3.2). Selection based on suggestion frequency provided some variation as to the types of cases represented. This allowed for exploration of contrasts in the analysis, but this was not critical. Potential issues with access to interviewees (indicated through the feasibility study) meant that there was insufficient scope for a case-constrained selection (where cases are purposively selected to ensure certain dimensions at play can be explored i.e. primary versus secondary care etc.). The intention was to complete, in no particular order, as many case studies as time constraints and accessibility to companies would allow.

Table 3.2: Short list of potential case studies (n=36)

Class	/Indication	Propitary name	Brand name	Company
PDE5 inhibitors	Erectile Dysfunction	Sildenafil Tadalfil Vardenafil	Viagra Cialis Levitra	Pfizer Lilly Bayer
Angiotensin II antagonists (Sartans)	Hypertension	Losartan Valsartan Eprosartan Irbesartan Candesartan Olmesartan Telmisartan	Cozaar + diuretic (Cozaar-Comp) Diovan Teveten Aprovel + diuretic (CoAprovel) Amias Olmetec Micardis + diuretic (Micardis Plus)	Merck Sharp & Dohme Novartis Solvay/(GSK) Bristol-Myers Squibb, Sanofi-Synthelabo AstraZeneca/Takeda Sankyo Boehringer-Ingelheim
Anti-Alzheimer's drugs	Dementia	Donepezil Galantamine Rivastigmine Memantine	Aricept Reminyl (mild to moderate) Excelon Ebixa (moderate to severe)	Eisai, Pfizer Shire Novartis Lundbeck
Atypical antipsychotics	Schizophrenia	Risperidone Amisulpride Clozapine Olanzapine Quetiapine Sertindole Zotepine	Risperdal Solian Clozaril Zyprexa Seroquel Serdolect Zoleptil	Janssen-Cilag Sanofi-Synthelabo Novartis Lilly AstraZeneca Lundbeck Orion
Thienopyridine antiplatelet $P2Y_{12}$ inhibitor	Stroke, MI, peripheral arterial occlusive disease, Ischaemic heart disease	Clopidrogel	Plavix	Bristol-Myers Squibb/ Sanofi-synthelabo
Interferons	Relapsing MS	Beta-interferon	Avonex Rebif Betaferon	Biogen Serono Schering Health
Statins	Reduction of cardiovascular events through lipid lowering	Atorvastatin Rosuvastatin Pravastatin Fluvastatin Simvastatin	Lipitor Crestor Lipostat Lescol + modified release (Lescol XL) Zocor	Parke-Davis/ Pfizer AstraZeneca Sqibb Novartis Merck Sharp & Dohme
Glitazones	Type II diabetes	Troglitazone Rosiglitazone Pioglitazone	Rezulin Avandia + metformin (Avandamet) Actos	Parke-Davis GlaxoSmithKline Takeda/Eli Lilly
Bisphosphonates	Osteoporosis	Alendronate Risendronate Disodium Etidronate	Fosamax + modified release (Fosamax Once Weekly) Actonel + modified release (Actonel Once a Week) Didronel + calcium carbonate (Didronel PMO)	Merck Sharp & Dohme Procter & Gamble Procter & Gamble

3.3. Gaining access to the Industry

3.3.1. Interviewee identification

For each case study, companies were approached in the order of market hierarchy position (market leader first). The diffusion curve data assisted in identifying the market hierarchy position for each drug within the class (area under the curve calculations

provided clarification if not evident from the curves). For a case study to reach a conclusion, agreement to interview was sought from a minimum of three companies within the class.

NIHR HSC contact

The NIHR HSC has regular contact with the Industry as part of its day to day conduct in order to obtain intelligence about future products in development. This level of prior contact provided a personal means of credibility as a researcher and aided the process of initial access. Email requests were sent to the named point of contact for case study drug companies from the NIHR HSC database requesting contact details of potential interviewees. A brief outline of the research was provided, stating that a more detailed description would be forwarded once an appropriate person within marketing had been identified (language and content were validated with Industry contacts prior to sending - see Appendix 4). Although the NIHR HSC database of company contacts could not technically be regarded as a sampling frame, it provided the basis on which the sample population was sought.

Industry contact

On receiving information from the NIHR HSC contact, potential interviewees were approached directly with a request to participate in the research (see Appendix 5). Citing the NIHR HSC contact as the person who had suggested them as an interviewee, increased researcher credibility. The research was summarised in an attached information sheet that also addressed likely questions interviewees may have had regarding the use of the information (see Appendix 6). It was also indicated at this point that while the company would be identifiable, no comments would be attributable to

particular individuals. The information sheet also served an additional function in that agreement to participate in receipt of this information was considered as consent on behalf of the respondent.

Characteristics of the sample

Interview participants required sufficient knowledge of the drug's diffusion history and had to be of a level of seniority to have the authority to speak freely about the topic without reference to others. This ultimately defined the characteristics of the participant and restricted the number of participants who could be included in the study. It was feasible therefore to conduct in-depth interviews with a smaller number of participants, and in doing so trade depth in one dimension i.e. all stakeholders' opinions about one drug, for breadth of knowledge in another i.e. using multiple case study drugs to explore one stakeholder's perspective.

The research request was addressed to the marketing directors of the companies involved. In addition to their position of authority, it was also accepted that the pharmaceutical industry is one in which there is a high turnover of staff and therefore it was unlikely that personnel could be identified who would have been present either within the same department, or even the same company, throughout the entire lifecycle of the case study drug. These were issues that had to be considered on an individual and pragmatic level, but personnel in directorate positions were considered more likely to have been in place for a sufficiently long enough period of time to recall the events under discussion. The interview population therefore comprised 'elite' professionals. These are a specific group of people with distinctive characteristics that had to be

accommodated during the access and interviewing stages (Duke, 2002; Ostrander, 1995) (for further details see Appendix 7).

3.3.2. Access process

Figure 3.2 outlines the access process with the pharmaceutical companies involved (see section 3.6.3 for further details on the pilot interview). Different levels of contact were required to achieve a response. In general, anywhere between five and 25 emails were necessary to set up an interview date from the point of initial communication with the NIHR HSC contact, to arranging a date for the interview with the respondent, or alternatively effecting a decline. Once respondents agreed to participate, there was often a short turnaround time to prepare for the interview.

On several occasions, the NIHR HSC contact (contact 1) unexpectedly acted as the 'gatekeeper' to access, often delaying the process by several months. No response to the initial email was followed up with a phone call to explain the details of the project. This was usually sufficient to secure the name of an interviewee if the blockage had arisen at the first step. If the blockage arose at the second step i.e. with the potential interviewee (contact 2), phone contact to discuss the project directly often secured an interview. By addressing participant concerns, which included issues such as source of research funding; eventual use of the data and need for prior sight of the questions, it helped to establish the trust required to gain access to potential respondents.

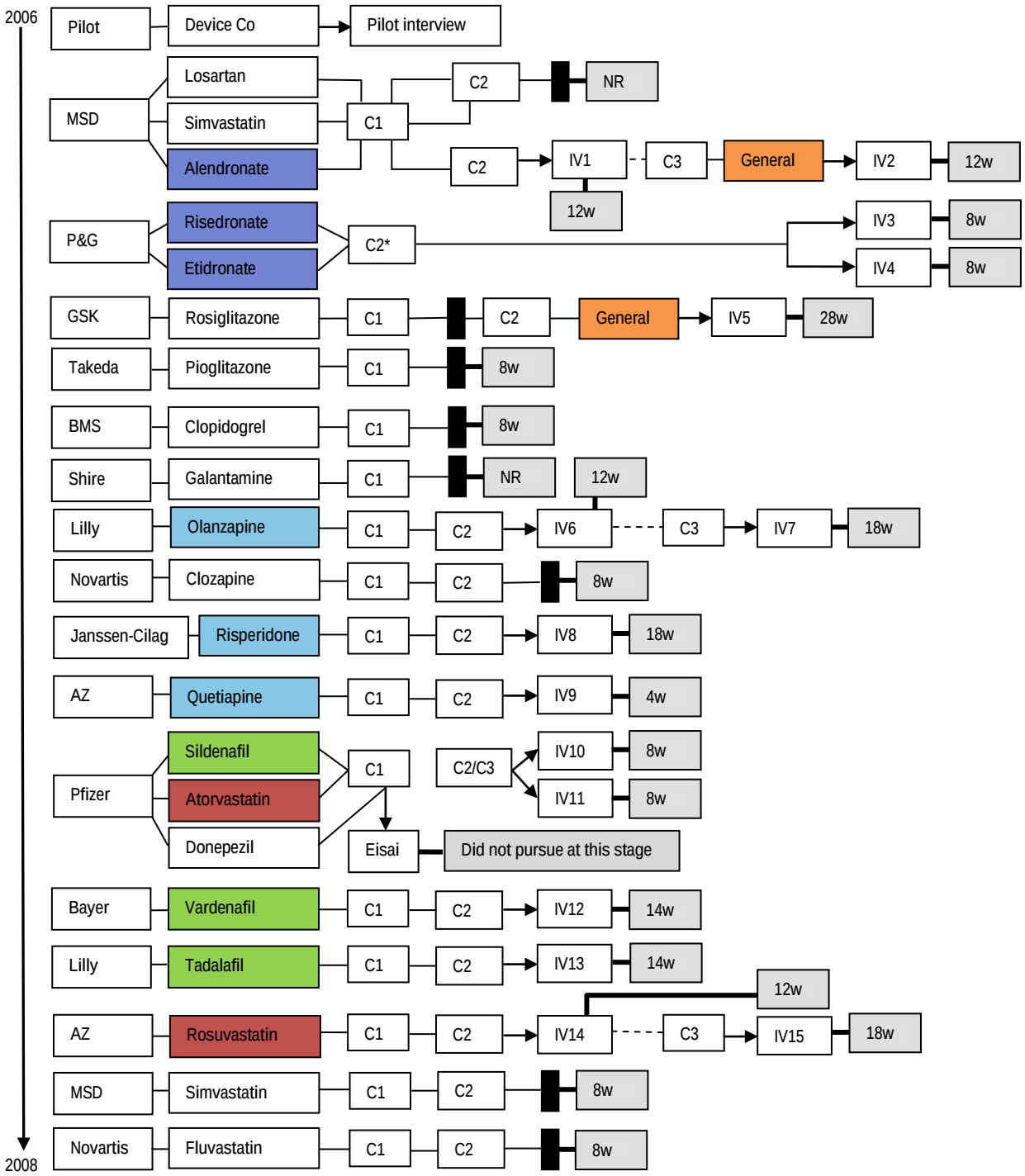
Refusal to participate occurred only on a few occasions. Reasons included:

- No personnel left within the company with the organisational memory recall;
- Would require several participants. Not possible to get them all together;

- Potential interviewee too busy;
- Case study drug still being marketed therefore information would be too sensitive;
- Case study drug deemed not representative of case study (intended for specific subpopulations rather than for main class indication);
- A second approach to a company for a different case study drug yielded the same nominated contact who had already declined to participate.

In some cases it was not possible to obtain a direct refusal to participate, but equally it was not possible to obtain agreement either. Despite efforts to reassure, contact and arrange appointments, in these circumstances it was necessary to progress to the next company in the market leader hierarchy for that class. Towards the end of the project this became more difficult as fewer companies remained who had not been contacted previously through prior case studies. Where blockages occurred at the second point of contact in the process i.e. potential interviewees, it was possible to recontact the same company again regarding a different drug i.e. could reapproach contact 1. However, if the blockage occurred at the first point of contact, any drugs involving that company could not be pursued. Explanations for why certain drugs in the case study pool were not pursued are outlined in Table 3.3.

Figure 3.2: Interview Access Process



Key:

C1 = Contact 1 (NIHR HSC Industry contact)
C2 = Contact 2 (potential interviewee)
C3 = Contact 3 (potential interviewee)
IV# = Completed interviews
▌ = Blockage to access (Co. unwilling/unable to participate)
--- = 2nd interview resulting from 1st interview
#w = No. weeks to agreement/refusal to interview from 1st contact

MSD = Merck Sharp & Dohme
GSK = GlaxoSmithKline
P&G = Procter & Gamble
BMS = Bristol-Myers Squibb
AZ = AstraZeneca
NR = No response
* = Industry contact of supervisor

Table 3.3: Case specific issues: Drugs not pursued

Case	Drug	Issues	Case decision
Statins	Pravastatin	Unable to pursue as received earlier refusal to participate in the research from Bristol-Myers Squibb regarding clopidogrel at the first contact point.	Statins included as a case on the basis of having completed 3 interviews (albeit on only 2 statins). Was not possible to obtain any further interviews for this class.
	Cerevastatin	Due to the withdrawal of cerevastatin after only four years, Bayer was not contacted regarding this drug.	
Glitazones	Troglitazone	Unable to pursue as GSK unable to discuss specific cases.	Despite completing the timeline and expert consultation, this case study had to be abandoned.
Anti-Alzheimer's drugs	Rivastigmine	Approach made to NIHR HSC contact, but no interviewee provided by Novartis.	Could not pursue case study as unable to secure interviews for 3 drugs from this class.
	Galantamine	No response from Shire.	
	Donepezil	Pfizer redirected to Eisai, but they were unable to provide a contact.	
Sartans	Losartan	No response from Merck Sharp & Dohme regarding losartan.	Earlier contacts/outcomes from other case studies compromised the availability of options in the hierarchy for this class (left 3 possible drugs). Having already reached data saturation with previous cases, coupled with time constraints and the unlikelihood of gaining agreement from all 3 companies, this case was not pursued further.
	Valsartan	Approach made to NIHR HSC contact, but no interviewee provided by Novartis.	
	Candesartan	Initial approach made to AstraZeneca, but redirected to Takeda. Could not pursue further as had been unable to involve Takeda at first contact point in relation to earlier case study (pioglitazone).	
	Irbesartan	Unable to pursue due to Bristol-Myers Squibb's refusal to participate in the research.	
Beta-interferons	Offered new companies, but case was not pursued due to time constraints and reaching data saturation with prior case studies.		

The final list of case studies is outlined in Table 3.4 together with summaries of the expert justifications for selection.

Table 3.4: Final Case Study Selection with Expert Justifications

	Case Study	Drugs Included	Company	No. interviews	Summaries of Experts' justification for case study selection
1	**Bisphosphonates**	Etidronate	P&G	1	BPs brought about a change in the definition of osteoporosis from a disease to a risk factor. Heavily promoted, directly to NHS staff and through provision of DEXA scanners in hospitals, and indirectly to the public about fear of hip fracture. Controversy surrounding the impact and benefit of BPs and where osteoporosis fitted as a risk alongside other factors in fracture prevention persisted due to delays in production of NICE guidance. Area of rapid increase in spend, especially since the demise of hormone replacement therapy as the treatment of choice for the prevention of osteoporosis.
		Alendronate	MSD	1	
		Risedronate	P&G	1	
2	**Atypical Antipsychotics**	Risperidone	Janssen-Cilag	1	Creation of a new class (AAs) marketed on the basis of fewer side effects was controversial as both the typicals and atypicals are an assorted group of drugs. Lively debate existed regarding their role in schizophrenia, their increased cost, unequal availability and emerging side effect profile compared to older drugs. High levels of patient engagement, formation of a patient group/professional and industry partnership promoted the needs of people suffering with schizophrenia, particularly with regard to quality of life issues.
		Olanzapine	Lilly	2	
		Quetiapine	AstraZeneca	1	
3	**PDE5 inhibitors**	Sildenafil	Pfizer	1	A very high profile class surrounded by immense publicity as the first oral treatments for erectile dysfunction. Raised numerous issues about cost, access, perception of erectile dysfunction as a lifestyle condition rather than a serious disease and became one of the few agents to be successful despite a lack of NICE guidance. Very heavily marketed both directly and indirectly to potential patients, but limited NHS availability restricted access and created tensions between secondary and primary care.
		Tadalafil	Lilly	1	
		Vardenafil	Bayer	1	
4	**Statins**	Atorvastatin	Pfizer	1	Statins had a profound effect on approach to prevention of cardiovascular disease and prescribing budgets. Surrounded by substantial promotion and now one of the largest prescribing areas with a huge cost to the NHS. Strong evidence for the class and specific drugs, but later entrants diffused without evidence of improved clinical outcome. Any resistance changed with the National Service Framework for Coronary Heart Disease. Side effect issues affected the class, resulting in the withdrawal of one molecule.
		Rosuvastatin	AstraZeneca	2	
	General interviews	-	GSK MSD	1 1	-

3.4. Diffusion curve construction

Data was obtained for all 36 potential case study drugs as diffusion curves were produced in advance of final case study selection. The diffusion curves provided a data set amongst others to triangulate against interviewee responses.

3.4.1. Data source: IMS Health

IMS Health is a global profit-making organisation that collects and interprets anonymised health information from a number of sources and provides information and consulting services to the pharmaceutical and healthcare industries and research organisations. IMS Health was approached in preference to any other pharmaceutical data agency primarily because of previous diffusion research collaborations with the NIHR HSC.

Data obtained

Following requests to IMS Health in November 2004, UK data was supplied from their retail and hospital databases in the format of drug strength; number of tablets per pack; number of units (UN) sold (equivalent to packs sold); per quarter from Q12 (December) 1992[2] to Q9 (September) 2004. The dataset was extracted from the IMS Health database by drug class, which enabled inclusion of all preparations, including those that had been previously withdrawn. Data updates were requested where necessary.

3.4.2. Data analysis

Data analysis took place between January and April 2005. In order to convert the data from a) number of packs sold[3] to b) use in patients, the World Health Organization

[2] The earliest date for which data was available.
[3] Retail and hospital units sold were combined to produce total usage of the drug in both primary and secondary care settings.

(WHO) classification system of Daily Defined Doses (DDDs) was used, as it is a recognised method of standardising patients from units sold.

The definition of a DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD system is used for presenting drug utilisation data as it allows for standardisation of drug groupings, enables comparisons of drug use between countries, regions etc. and enables the examination of trends in medicine use.

DDD measures for the case study drugs were obtained in December 2004 from the WHO Collaborating Centre for Drug Statistics Methodology website www.whocc.no/atcddd/ using the Anatomical Therapeutic Chemical (ATC)/DDD Index 2005 and searching via the drug name. Drug usage in terms of number of DDDs was calculated from the data as outlined below:

$$\textit{Drug usage (No. of DDDs)} = \frac{\textit{[Concentration (mg/tab)] x [n tablets per pack] x [n units sold (UN)]}}{\textit{WHO Daily Defined Dose Measure}}$$

Limitations of DDDs

Diffusion curves based on DDD calculations are commonly used in diffusion studies, but they have to be considered within the context of their limitations. DDDs can be regarded as a crude method with obvious dangers of over-interpretation. They are based on the average daily therapeutic maintenance dose of a drug used for its main indication and therefore do not reflect the variations in dose if the drug is used for different indications. It can therefore only give a rough estimate of consumption (Clarke and Gray, 1995). An additional caveat to the DDD system is that in its attempt to determine

an internationally universal value, the DDD could have potentially changed over time, although most modifications are recorded pre-2000. In this context however, DDDs were not being used to compare data on actual drug consumption, but as a relative measure to be able to achieve the shape of the curves. Alternative measures were considered, such as Prescribed Daily Dose (PDD), which is the average daily dose of the drug in the population with the disease of interest, but PDDs require that the treatment is specific to the disease and that the drugs are taken all year. As some of the drugs under consideration as case studies were not exclusively for chronic use, DDDs were chosen as the preferred unit. The use of direct sales data was also deemed unsuitable as firstly, it is subject to inflationary changes which would have to be accommodated for and secondly, it is not possible to identify when a product becomes generic, whereby usage could increase vastly, yet there would be little impact seen on the sales curve due to the significantly reduced price of the generic version.

Due to the nature of the way the data was supplied, an additional limitation of the diffusion curves is that any impact from an event would not be evident until the next reported quarter. If several events occurred within the same quarter, it was not possible to distinguish their individual effects. Despite these inadequacies, the DDD approach achieved the desired aim, which was to demonstrate where the relative inflexion points occurred during the drug's lifecycle to stimulate discussion with Industry respondents. It was not necessary to demonstrate exactly where the inflexion points occurred using time series analysis methods as the intention was for the respondents to identify where they perceived the inflexions to be as opposed to influencing their decision.

3.4.3. Diffusion curve construction

Individual diffusion curves representing drug usage (in terms of number of DDDs) over time were plotted for each of the potential case study drugs. Area under the curve calculations indicated the market hierarchy position of each drug within its class.

3.5. Timeline construction

3.5.1. Literature-based timeline

To augment the diffusion curves, a timeline of events potentially affecting the diffusion of the case study drugs was constructed from a review of the background literature. This was used as a triangulation source that could be compared with the diffusion curve and Industry-derived accounts of the same phenomenon. It was also an essential process of familiarisation of the topic material ahead of the interviews to enhance my credibility as a researcher amongst an elite participant sample. It was not an attempt to systematically document all activities that impacted upon the diffusion curve, but to reflect some of the main events prioritised with clinical expert input (see section 3.5.2).

Information was sought mainly through internet search engines using key words or through MEDLINE/EmBASE and EconLit searches, drug pipeline development databases (PharmaProjects - Informa Healthcare [www.pharmaprojects.com]; Adis R&D Insight - Springer International Publishing AG [www.adisinsight.com]) and national and international clinical guideline finders, analyst reports and the Cochrane Library. Search terms included keyword searches of the drug's generic and proprietary brand names, and specifically looked for any controversial events throughout the lifecycle; marketing campaigns; comparative reviews; pivotal trials; significant clinical guidance; health policy issues; systematic reviews; historical research and development

reports; launches of new formulations, or additional licence indications (See Appendix 8).

3.5.2. Clinical expert augmentation

The validity of the literature-based events were reviewed and augmented by case specific clinical experts in a one to two hour interview prior to conducting the Industry interviews. This was to 1) validate the findings of the case specific literature search and 2) to provide any additional insights in preparation for the interviews with the Industry. As the intention of the research was to obtain Industry perspectives, the timelines were not shown to the interviewees at any stage so as to not influence their accounts by providing pre-identified events. They were however, later used as an additional data source for triangulation alongside the interviewee accounts and the diffusion curves.

Experts were identified through snowball sampling, either through clinical contacts of one of my supervisors, or if they were unable to participate, they would suggest other colleagues. Experts were approached as soon as one company within the class had agreed to participate, which meant that the expert and background work had to be completed without the knowledge the case study would reach completion. This also resulted in a short turnaround time to complete expert interviews.

Expert augmentation was considered a more preferable method of validating the literature-based explanations for the curve inflexions, compared to time and resource intensive techniques such as interrupted time series analysis where events either side of a data point are analysed to determine if an event was responsible for causing that inflexion. It was considered inappropriate to force such quantitative rigour onto a project that was concerned with perceptions and beliefs. The research aimed to capture where Industry respondents perceived these inflexions to be, not necessarily where they

were proven to be, and what they thought were the most likely explanations for the perceived inflexions. Case studies that lacked or had limited expert input relied more on the literature to justify inclusion of events in the timeline.

3.6. Industry interviews

Interviews were conducted with 15 participants from eight pharmaceutical companies.

3.6.1. Semi-structured interviews

To study perceptions that are representative of an organisation or individual requires methods that can reveal the depth of insight into what is said by respondents. Perception is by definition, the process by which someone interprets the actions of the external world. Questionnaires are too rudimentary to offer this level of depth, particularly when dealing with such a sensitive research subject often protected by 'commercial in confidence' caveats. This project required more subtle methods that enabled the building of trust between researcher and respondent.

Interviews are one of the most important sources of case study information, as they are particularly appropriate for exploratory research to study the range and complexity of ideas and definitions used by respondents. They often enable access to private accounts, particularly when addressing sensitive subjects. They also allow participants more opportunity and time to express their views and opinions compared with other methods of qualitative data collection. In fact, such an in-depth understanding of the participant's point of view cannot be achieved using any other data collection method (Hansen, 2006). While it is appreciated that interviews do have inherent problems in that they rely upon individual interviewee reports likely to be constrained by the context in which

they are collected, these limitations are considered acceptable if the aim is to understand individuals' perceptions. When interviewing people in positions of power, a semi-structured question format is considered to be far more effective than unstructured or highly structured interviews, as they tend to tip the balance of power in favour of the researcher (Walford, 1994; Ostrander, 1995; Hirsch, 1995).

3.6.2. Interview schedule

An interview schedule is a list of broad key areas to be covered during the interview along with a selection of open-ended questions relevant to each topic area designed to encourage a thorough response. It provides a visual reminder of the key subject areas to cover if the interviewee deviates away from the intended sequence of topics (a feature of the unstructured nature of a semi-structured interviews), and ensures the same topics are covered during each interview.

Interview schedule structure

The interview schedule (provided in Appendix 9) was developed in conjunction with the access materials. The questions were grouped into sections according to *a priori* knowledge of diffusion influences with introductory statements that explained the function of that particular set of questions. The schedule started with a statement of purpose and a series of general questions to settle the respondent into the interview, before progressing to specific case study questions about their understanding of, and attitudes towards critical factors they felt explained the inflexions in the diffusion curves of their company's drug. Signposting statements were used throughout to communicate a structure to respondents as the interview progressed.

Question structure

The number of questions was determined as a function of the proposed interview length. The literature indicated that a semi-structured interview of 45-60 minutes would support around 10-12 interview questions (Hansen, 2006). Questions were constructed mindful of the fact respondents were participating through goodwill. It was essential to maintain that basis in broaching difficult subject areas or in reaction to 'official line' responses, by using a recognised interview technique that asks respondents about the opinions or behaviour of other people, such as "some people believe that ...What's your view?" which enables disassociation of a potentially provocative view from that held by the researcher (Ostrander, 1995; Duke, 2002).

Questions were:

- open-ended to encourage a detailed response from respondents and reveal possibly unanticipated viewpoints (avoidance of closed/leading questions);
- kept to individual concepts/unambiguous in their wording (emphasis on the use of spoken English as opposed to written English);
- non-threatening/non-controversial at the outset;
- designed to incorporate appropriate vocabulary (validated by Industry contacts prior to use as considered important when dealing with elite respondents);
- asked in such as way as to achieve equivalence of meaning with individual respondents rather than imposing standardised questions throughout.

It was necessary to establish credibility with participants by asking relevant questions that were perceived as meaningful by the interviewee and that were based on an understanding of the research subject, as supported by Legard *et al*. (2003).

3.6.3. Pilot interview

The pilot interview gave the opportunity to trial and refine the interview schedule, whilst providing a forum for qualitative interviewing practice. The pilot was conducted with a former marketing director of a medical device company using implantable cardioverter defibrillators as the case study subject. The pilot interview took place before it was known which pharmaceutical companies were going to be involved in the research and therefore a non-pharmaceutical company was chosen so as to not jeopardise any of the potential case study drugs. The questions could be easily adapted to suit a medical technology, whilst still being able to identify any potential issues with the nature of the questions.

The pilot interview was conducted in May 2006. As with the case studies, a diffusion curve and timeline of events was generated, but the respondent only had access to the unannotated diffusion curve during the interview. Suggestions for improvement included a need for clearer signposting during the interview, provision of a pre-interview agenda to allow participants sufficient time to consider the questions properly and emphasising the fact that it was an academic and not a journalistic exercise to make respondents aware that breaking away from the 'official line' would not be detrimental. It was also highlighted that it would not be considered offensive to use direct or controversial prompts as this interview population would be experienced in dealing with this line of questioning.

3.6.4. Interview Participants

Despite a consistent approach in the way requests were made to companies with regard to interviewee profiles, participants had an extensive range of job titles. They were predominantly from within the marketing departments for the specific brands of drug, or disease area business units, but also included participants from more general areas of the companies including market access, government affairs or managing director level. While this variation ultimately impacted on the content of the interviews (consistent with the literature (Duke, 2002), those respondents of higher seniority were less guarded in their responses), the companies had selected the person they deemed the most suitable to participate in the research. Also consistent with Duke's observations was that some respondents were either conducting research projects themselves, or had done so in the past as part of their professional training, which may have been a factor in their willingness to participate.

On two occasions snowball 'convenience' sampling (where the interview participant suggested another person who would be useful to contribute to the case study discussion) led to subsequent interviews. While acknowledged as a sub-optimal sampling method, it was a pragmatic response to access difficulties and is not an uncommon practice in studies involving Industry participants.

3.6.5. Pre-interview materials

Respondents received an unannotated diffusion curve for their product under discussion in advance of the interview, but did not have access to the literature/clinical expert augmented timelines before or during the interview. Initially, participants were also

provided with a signposting agenda on the basis this would reassure them as to the direction and scope of the interview. However, after the second interview it became apparent that agendas changed the balance of power in favour of the respondent by enabling prepared responses and personal agendas that were difficult to steer away from. They were discontinued in subsequent interviews in favour of verbal signposting.

3.6.6. Interview conditions

Interviews took place between July 2006 and May 2008. Interviews were conducted solely by the researcher on a one to one basis at the interviewee's place of work. Interviews lasted on average around one hour (range 45 minutes to 1 hour 50 minutes) and were digitally recorded to allow for accurate capture of the data following interviewee consent. Whilst introducing the project it was often necessary to explain the term 'diffusion' which seemed to be a term more closely associated with academic research rather than that routinely used in pharmaceutical marketing.

The interviews covered general and case study specific themes, with the emphasis on enabling respondents to give spontaneous accounts of their perspectives on events they felt were most significant in affecting the diffusion curve for their product over its lifecycle and its competitors. The semi-structured format provided enough scope for respondents to talk freely around certain key themes and identify issues they felt were important that could then be pursued through new lines of questioning.

It is accepted in the literature that interview schedules are dynamic as they reflect ongoing data collection and analysis (Hansen, 2006). Although the main topic areas remained constant, slight modifications were made during the course of the study period based on experiences of previous interviews. The most significant change was related to reducing the time allocated to the 'general' sections of the interview to allow

for greater exploration of the specific case study issues, as interviewees tended to draw on specific examples to respond to the general questions.

3.7. Thematic analysis of the interview data

Invariably, interview data in its text form is unwieldy and unstructured, with highly detailed content. A coherent structure has to be applied to the data for it to become meaningful without losing the original accounts and observations from which the structure is derived (Ritchie and Spencer, 1994). Thematic analysis i.e. analysing the data across case studies by theme enabled a generic set of Industry views on diffusion factors to be elucidated. A thematic approach also removed some of the sensitivity issues surrounding individual drug narratives.

3.7.1. Thematic frameworks

Thematic frameworks provide the analytical tools to classify and organise data according to key themes, concepts and emergent categories. According to Ritchie and Spencer (1994), this process relies on the "conceptual ability of the analyst to determine meaning, salience and connections". Framework is a particular thematic framework developed by Ritchie and Spencer (1994) and is a well-recognised method of qualitative analysis used in health services research. Framework starts deductively from pre-set aims and becomes more inductive as respondents' themes emerge i.e. inductive refinement of existing analytical categories (Pope *et al*., 2000). A conceptual model relevant to the question is chosen and used as the basis of the initial coding framework (themes or concepts identified *a priori* can be specified as coding categories from the outset). The extensive volume of prior work on diffusion, including Rogers' Diffusion

of Innovations theory meant that Framework was an appropriate method to use in this analysis.

3.7.2. Stages involved in Framework analysis

Framework analysis uses the standard qualitative approach of reading and re-reading the transcripts and selecting and reorganising responses according to themes, but data collection is more structured than would be the norm for other qualitative research. It uses a matrix-based method involving the construction of thematic categories into which data can be coded, enabling the analytical process to be more explicit (Dixon-Woods, 2011). As more transcripts are included, the list of themes subsequently reduce by merging the subgroups into more useful groupings. The final product is a revised framework containing both modified factors and new factors that were not anticipated in the original model. This process is described according to five distinct, yet highly interconnected stages of familiarisation, identifying a thematic framework, indexing, charting and mapping and data interpretation (see Table 3.5).

Table 3.5: The analytical process according to 'Framework' stages

Framework Stages	Theoretical description
Familiarisation	*A priori* issues are founded. Immersion in a selection of the data through: • listening to recordings • reading and re-reading transcripts • noting key ideas and recurrent themes Start at an early stage and repeat, whilst still collecting data.
Identifying thematic framework	First version is heavily rooted in *a priori* issues and largely descriptive. Apply framework to a few transcripts. Refine categories - look for conceptualisations that encapsulate experience; attitude; circumstance. Framework becomes more responsive to emergent themes.
Indexing (coding)	Systematically apply the thematic framework to individual transcripts. All data read, and annotated by numerical system corresponding to framework categories (margins). A paragraph may contain several themes (multiple indexing). Highlights patterns of association. Indexing is a subjective process and open to differing interpretations.
Charting	Build up a picture of the data as a whole. Data is 'lifted' from original context and rearranged according to the appropriate thematic reference (text grouped together with the same thematic code). The chart headings can be laid out according to whether analysis is to be: • thematic (for each theme across all respondents) • by case (for each respondent across all themes)
Mapping / data interpretation	Pull together core themes: **charting** – looking for themes. **mapping** – how themes relate to one another (conceptualisation). • Define concepts • Range and nature of phenomena • Creating typologies • Finding associations • Providing explanations • Developing strategies

3.7.3. How I carried out the Framework analysis

The bisphosphonate case study interviews were completed first. Initial thoughts on key themes raised by respondents were noted immediately post-interview. Interviews were professionally transcribed verbatim, but due to time constraints and resolving access issues for subsequent cases, the coding process did not take place until after completion of the second case study (the atypical antipsychotics). Insights from notes and listening to the interviews from the first case study however, were used to iteratively develop the interview schedule for the second case study to pursue any new theories that had emerged.

Atypical antipsychotics (AAs)

On completion of the second case study, the coding process began. A manual version of thematic analysis was used in favour of software packages, such as NUDIST or NVIVO on the basis that as a novice qualitative researcher on a project of this scale, it would enable a comprehensive understanding of the distinct processes involved and explicit representation of how conclusions were reached.

- Familiarisation (data immersion)

Coding of the AA interviews took place first, but before sifting and sorting the data, it was necessary to get what is often described as a 'feel' for the data. The recordings from the AA interviews were listened to repeatedly and the transcripts verified for accuracy against the original recordings. Key ideas and recurrent themes which emerged as important to the respondents themselves were annotated on each drug's diffusion curve. These narratives (referred to as drug-specific accounts) provided the third data source used to triangulate against the diffusion curve and the literature and expert augmented timelines (described in Chapter 6). These exercises provided a starting point for identifying the major anticipated (theoretically-informed) and emergent themes rather than using the transcript as a first strategy to coding and began the process of abstraction and conceptualisation.

– Identifying a thematic framework (developing a coding frame)

Notes were made in the margins of the transcripts, assigning quotes in the first instance to the broad *a priori* categories informed by the literature review and the substantial existing body of work on diffusion such as 'Evidence', 'Communication channels', 'Drug characteristics' etc. However, these were not arbitrarily imposed on the data. The

subthemes and new categories that had started to emerge during the familiarisation stage were further developed to reflect any new insights offered *(in vivo* codes). Margin notes were collated, discussed with one of my supervisors and sorted into categories and subcategories. The resulting framework, referred to as the 'post-coding' framework consisted of a mixture of key themes reflecting the aims of the research and introduced into the interviews via the topic guide, as well as those emerging from the data, and analytical themes arising from the recurrence or patterning of particular views or experiences.

– **Indexing (Coding the data)**

The codes from the post-coding framework were applied to the four AA transcripts (two of the four interviews related to the same drug, but were from different personnel within the same company).

– **Charting (cut and paste)**

Coded extracts were electronically 'cut and paste' from the transcripts and collected under the corresponding coded headings in an excel spread sheet according to company to undergo data interpretation.

– **Initial mapping and data interpretation**

Once all of the data from the AA case study had been charted, the quotes were transferred into individual word documents according to theme. Descriptions were then written to define the theme and any emerging ideas about the data. As a result of doing this process, the framework could potentially adapt again as quotes were reorganised ('post-analysis' framework). This was the start of the mapping and interpretation process that continued to be refined as more data was added.

Bisphosphonates (BPs)

At this stage it was not clear if separate frameworks would be appropriate for each case study and so the BP coding and charting processes were conducted independently of the AAs. While some of the key themes from the AA framework were used to inform the BP framework, it was mainly influenced by the BP data and the analysis was also considered separately from the AAs.

PDE5 Inhibitors

As a result of the similarity between the framework categories from the first two cases, the decision was made at this point to merge the AA and BP frameworks to develop a single 'global framework' that accommodated all the data so far. This provided a 'starter for ten' for the next case. Any new insights to pursue were incorporated into the topic guide ahead of the interviews on the PDE5 inhibitors. The PDE5 inhibitor interview data was then coded against the merged AA and BP framework. New material further challenged the emerging coding framework, which was flexible enough to be adapted and refined as categories and subcategories were re-thought (the resulting framework incorporated themes from all three cases – referred to as the BP+AA+PDE5 post-coding framework). Ritchie and Spencer (1994) described how, "devising and refining a thematic framework is not an automatic or mechanical process, but involves both logical and intuitive thinking. It involves making judgements about meaning about the relevance and importance of issues and about implicit connections between ideas". The data from the previous two cases and the new case were charted according to the new framework structure on a single spreadsheet and analysed collectively, giving rise to further modifications to the framework (BP+AA+PDE5 post-analysis framework) as the analytical interpretation developed with each new case.

Statins case study and general interviews

Once the final case study (statins) was completed, this data together with the general interviews conducted earlier in the process was coded against the BP+AA+PDE5 post-analysis framework to generate the (BP+AA+PDE5)+statin+general post-coding version of the framework. The two interviews that covered general as opposed to case specific information were listened to and only material relevant to themes identified from the case study interviews was extracted i.e. supported existing themes, added new perspectives, or provided disconfirming evidence. The new data fitted into the previous version of the framework without significant alteration i.e. no new perspectives were uncovered, suggesting theoretical data saturation was being achieved.

Disconfirming evidence – Throughout the process, negative cases (disconfirming evidence) were sought and incorporated into the analysis i.e. if part of transcript did not fit within one of the framework categories derived from the interviews so far, that category could be expanded using a different theme description to encompass the new piece of data. If this was not appropriate, then a new category would be formed, which could be absorbed into another theme at a later stage once more data fed into the framework (an example is provided later in section 3.8.1).

A worked example showing how the coding framework developed throughout the analytical process for theme 3 ‘Clinical evidence (Efficacy)’ is presented in Figure 3.3. The assignment and re-assignment of direct quotes to the iteratively derived coding categories for this particular theme is presented in Appendix 10.

– **Mapping and data interpretation**

Although the analysis was developed throughout the coding and charting stages, the final framework (BP+AA+PDE5+Statin+general post-analysis framework) was produced following analysis of the data as a whole. This stage addresses the key objectives of the qualitative analysis. This involved pulling together key characteristics of the data, mapping and interpreting the data by comparing and contrasting the perceptions and accounts, searching for patterns across the data and associations within it and seeking explanations for these internally within the data. As outlined by Ritchie and Spencer (1994), the type of analysis route is guided by the original research question and by the themes and associations which have emerged from the data. The analysis, which is presented in Chapter 5, is structured according to the ten major themes of the final framework to provide explanations as to the reasons why pharmaceuticals diffuse or not from the perspective of Industry respondents. In doing so, it also illuminated Industry respondents' attitudes, experiences and behaviours.

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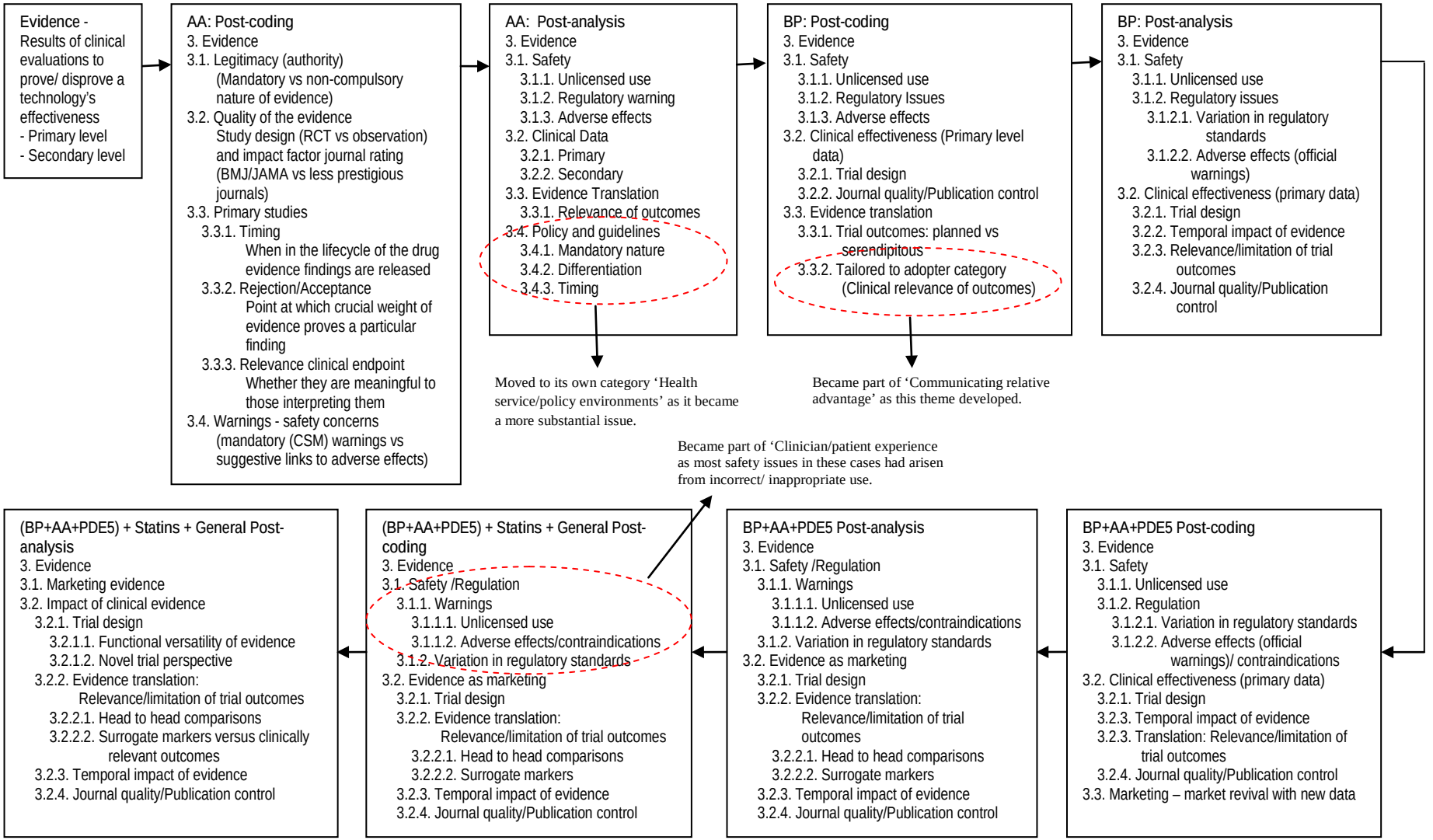
Figure 3.3: Iterative development of the coding framework for the 'Clinical evidence (Efficacy)' theme
(equivalent figures for the other 9 themes can be found in Appendix 11)



3.8. Quality assessment in qualitative research - strengths and limitations

Qualitative research is often criticised for being an assembly of anecdote and personal impressions, strongly subject to researcher bias due to the degree of inference required to explain meaning, resultsing in research that lacks reproducibility (Mays and Pope, 1995; Madill *et al.*, 2000). Qualitative methods generate large amounts of detailed information about a small number of settings, and although statistical inference is not the objective of qualitative research it is often criticised for lacking generalisability. The results of this study must be interpreted in light of its limitations, but it is important to highlight that objectivity and reliability are understood differently in qualitative research (Houghton *et al*., 2013).

Key questions in assessing the quality of qualitative analysis (Green and Browne, 2005) include:

- How does the reader know these findings are not just the subjective interpretation of the researcher?
- How does the reader know the researcher has not just picked out the examples that support their hypothesis?
- The sample is very small – how does the reader know these participants are representative of a larger population?

Kirk and Miller (1986) demonstrated how quality in qualitative research can be assessed in equivalent terms of reliability and validity as those employed in quantitative approaches (see Table 3.6).

Table 3.6: Validity, reliability and generalisability in qualitative and quantitative studies

Concern	Quantitative approach	Qualitative approach
Does the study investigate what it aims to do?	*Internal validity:* Good study design; the extent to which alternative explanations of causal relationships are explored and taken into account.	*Credibility:* Triangulation of data to explore extent to which a full picture of complexity is achieved; examination of 'negative' or disconfirming cases (allow refining of categories); theoretical saturation (are concepts well rounded?).
How broadly can the results be applied?	*External validity* (generalisability): Large representative random samples, with statistical inference of results to defined populations.	*Transferability:* purposive or theoretical sampling and discussion of choices made; results are descriptions applicable within a specified setting (is the setting representative of the population to which generalisation is sought); demographic material describing the context of the study is helpful.
How is bias avoided?	*Objectivity:* Attempt to control all sources of bias in order to arrive at an objective view.	*Reflexivity:* Assessing the effect of the researcher at every step. Bias arises where the effect of the researcher is ignored. Preconceptions and prior theoretical perspectives declared and explored.
What degree of certainty can we have of the results?	*Reliability:* The extent to which a test/measure yields the same result in repeated applications i.e. replication.	*Reliability:* Transparency and accuracy measures; respondent validation of results.

Mays and Pope (1995) operationalised the set of concerns outlined in Table 3.6 in the form of a checklist against which the quality of qualitative studies can be assessed providing they adequately address the components described in the checklist (see Appendix 12).

3.8.1. Credibility (internal validity)

Comprehensiveness - Data from all of the case study interviews was coded and charted and interpretations accounted for all extracts under each thematic heading. The reader has access to the majority of quotes in Chapter 5, apart from circumstances where there were instances of repetition and the best exemplifying quote was presented.

Thoroughness (disconfirming evidence) - Analysis was driven by comparisons between and within cases. Analysing why things were the same or different provided the basis on which to find out what respondents believed were influential drivers and barriers to diffusion. Disconfirming evidence to emerging theories was constantly sought throughout the analysis. It was not forced into categories or ignored, but was

incorporated into the analysis to aid understanding and refine theory development, or sometimes led to reconceptualisation of themes. An example included the impact of safety concerns. Most respondents considered safety issues regarding their drug as being detrimental to diffusion, but in the case of sildenafil, the fact that a contraindication had been identified was viewed by a respondent as having a positive impact. It acted to reassure patients that the drug had been fully tested and they could be assured of its safety profile in amongst a backdrop of publicity suggesting potential safety issues.

Study Design (Case study approach/semi-structured interviews) – While it placed constraints on the research, particularly since the results were then de-contextualised and presented thematically, the case study approach was instrumental in getting beyond 'official line' responses. They provided real life contexts from which interviewees could draw upon examples. Compared with theoretical discussion of general factors, case studies enabled triangulation of accounts with other data sources of the same phenomenon to test validity and reliability of the empirical findings (in accordance with a constructivist approach however, it is inappropriate to consider that triangulation constructs an ultimate 'truth' of the case study story, but instead provides an enriched picture of events).

Interviews elicited a depth of response through established rapport that would not have been achieved through written responses. The advantage of using a semi-structured approach was that similar data could be gathered from all respondents, which was useful when taking a thematic approach to the analysis. It is acknowledged however, that in talking a semi-structured approach, *a priori* knowledge influenced the analytical themes derived from the data (at least initially) through the questions posed. A more

experienced qualitative researcher may have been able to have avoided this bias by being able to explore simply ‘what factors affect diffusion?’ which is likely to have elicited more fully the views and priorities of the respondents, but this would have been a high risk strategy with this group of respondents and the nature of the research topic.

Social acceptability bias – When research of this nature has been conducted with adopter groups, social acceptability bias has been highlighted as a limiting factor. Clinicians may be reluctant to reveal some of the more irrational explanations behind their prescribing decisions that may not be in alignment with current practices or be judged as socially unacceptable by their peers. There is a certain freedom that comes with discussing another professional groups’ behaviour that would not be readily divulged by members within that group. As adopters are often keen to discuss Industry behaviour, respondents were equally prepared to discuss behaviours of clinicians and payers that were perceived by them as being influential in diffusion, which has offered a new insight into this area of research.

Triangulation – Credibility can be enhanced with triangulation, which uses several methods to study one phenomenon. The three triangulated data sources in this research included the case specific i) diffusion curves, ii) literature and expert timelines and iii) individual drug-specific narratives developed through annotation of the diffusion curves from respondents accounts generated during the familiarisation stage of the analysis. The purpose of triangulation was to ensure the data was complete through gathering multiple perspectives from a variety of sources. Points of convergence are not claims of truth, but instead provide the context for discussion of differences, which enhances completeness. Exploration of the divergent understandings then generates an enriched picture of the phenomena (Casey and Murphy, 2009). Some of the concerns around

cross contamination of the data during triangulation are addressed in the section on reflexivity in section 3.8.2.

Single analyst/ Peer debriefing (multiple coding or inter-rater reliability) – As the subject of a Ph.D., multiple researcher coding was not possible. While consistency can be enhanced by a single analyst, it does increase the chance of missing important issues or being funnelled into narrow interpretations as no two researchers will interpret the data in the same way. Reflexivity was therefore particularly important to acknowledge how my pre-conceptions may have impacted on data interpretation. Ryan-Nicholls and Will (2009) recommend using peer debriefing, where the aim is not for another analyst to arrive at the exact same coding and thematic structure as the researcher. Rather the purpose is to see if they agree with the data coding and the logical paths taken to arrive at those codes (Graneheim and Lundman, 2004). While no one else coded my raw data, discussions were conducted throughout with one of my supervisors regarding the coding frame I had developed to determine if it was a plausible interpretation.

Member checking (respondent validation) – Credibility can be enhanced by giving respondents the opportunity to validate their input for accuracy and interpretation. There is debate however, at what point in the research process this should occur. If respondents are shown the verbatim transcripts, they will be able to acknowledge and respond to their own words, but they will have no contribution to how their opinion and assertions are interpreted and portrayed (Koch and Harrington, 1998). If respondents read the construction derived from the analysis, this brings different challenges (Koch, 1994). Respondents will not be able to recognise themselves or their particular experiences if the study results have been synthesised, decontextualised and abstracted from individual participants (Sandelowski, 1993; Morse *et al.*, 2002). This was a

particular issue for this research project as the time taken to complete all case studies to achieve across case analysis meant that it was not possible to contact all those involved (feedback on individual transcripts or interim analyses would have been of limited value due to the evolving nature of the framework). Providing the individual transcripts could have also posed a risk of participant veto ahead of case study completion due to the sensitive nature of the content. The lack of member checking is recognised as a limitation in this research, but one that was particularly difficult to avoid.

3.8.2. Dependability and confirmability (reliability/objectivity)

Audit trail (transparency and accuracy)

To assess the trustworthiness of a study it is necessary to examine the process by which the end-product has been achieved (Houghton *et al*., 2013; Bryar, 1999; Ryan-Nicholls and Will, 2009). Providing details of the steps between data collection and interpretation can improve the quality of qualitative research as it enables the reader to see how the analysis was carried out. Through the provision of raw data, even if a reader does not share a researcher's interpretation, they are able to discern the means by which it has been achieved.

In this study, interpretation bias was minimised with verbatim transcription of recorded interviews (i.e. data captured as described by respondents). The Framework method is also an explicit analytical process with thorough and systematic coding of the raw data which enables people other than the researcher to view and assess the analysis. Extensive amounts of raw data were included in Chapter 5 to justify analytical conclusions and a worked example for one of the themes, showing how quotes were

assigned and reassigned to new coding categories as they informed new concepts is available in Appendix 10. The interview schedule outlining the broad subject headings discussed is provided in Appendix 9.

Reflexivity

Reflexivity acknowledges the way in which a researcher and the research process have shaped the collected data, including the role of prior assumptions and experience, which can influence inductive inquiries. Mauthner and Doucet (2003) have criticised the fact that many qualitative studies simplify the complex processes of representing the 'voices' of respondents "as though these voices speak on their own, rather than through the researcher who makes choices about how to interpret these voices and which transcript extracts to present as evidence". A constructivist perspective acknowledges that the researcher is part of the research process. Credibility is therefore enhanced if the researcher is self-aware of the multiple influences they have on the research processes and can demonstrate how their theoretical perspective may have affected data collection and interpretation (Toffoli and Rudge, 2006).

Researcher biography – As a female scientist working within a medical context, I shared similar educational and professional characteristics with those of the interviewees, several of whom were also holders of higher degrees. The privilege of being a Ph.D. student however, was that it afforded a non-threatening status. The interviewee population was of mixed gender, and were either of a similar age or older than myself. As an employee of the NIHR HSC, which is an organisation that interacts with the pharmaceutical industry and NICE, I had an appreciation of the culture in which the interviewees operated, although differences inevitably existed between

myself and interviewees shaped by their commercially-driven, as opposed to my academic influences.

I came to my PhD with a positivistic background in toxicology. As such, I did feel a positivist pressure to render my voice and my influence invisible to the research, presenting a neutral, detached 'objective' view. My biography impacted upon the choice of methods that guided the research initially, preferring Yin's positivistic approach to case study research that was more consistent with the paradigm with which I was familiar, rather than Stake's more constructivist approach. Over the period of time during which I have conducted the research, I have felt caught between the two paradigms, identifying tensions and contradictions that exist in order to justify my fluctuation between the two positions. I have a shifting perspective, taking more of a positivist position on some questions (related to the material world) and a more relativist position on others (those that involve social phenomena).

As the research and the analytical process have progressed, I have recognised how my involvement as a researcher has shaped the process, leading me more towards the constructivist position. Unlike empirical scientific studies the outcome of this research would probably have been different had it been conducted by someone else. Therefore, it feels inappropriate to attempt to present a detached view. The aim was not to uncover an ultimate truth, but to present one perspective amongst many others on this research subject, with the acceptance that reality is constructed differently depending on who is looking at it and from where. The presentation of my respondents' reality was influenced by how my experiences have led to particular ways of 'seeing' and 'hearing' the data during the analytical process.

Reflections on the research process

Access process

There was an awareness of the potential difficulties of gaining access and appropriate measures were taken to increase chances of success. These are outlined in section 3.3 (details provided on tailoring language, measures to alleviate respondents' concerns etc.). From a personal perspective, while it was anticipated that gaining access would be challenging, it could be very frustrating at times and required persistence to gain agreement. This was particularly true when cases had to be pursued without the knowledge they would come to completion. Being conscious of respondents' concerns, particularly with regard to the use of the data and identity issues, helped to secure their participation. In other cases where companies were showing signs of reluctance, it sometimes proved useful to highlight that they stood to be the only company within that class not to participate in the research.

Interview process

Use of agendas – The research process was responsive to problems as they arose. As discussed in section 3.6., the use of an agenda that was advocated during the pilot interview was substituted for verbal signposting as I felt respondents were driving through the agenda with what seemed like prepared responses rather than expanding on the issues to be covered. In the subsequent interviews, I decided to use verbal signposting, which helped to shift the balance of power in my favour. The responses of the interviewees appeared more considered as they often took longer to respond. At these points, the use of silence on my part was useful to give respondents time to think

before responding. As much more insightful discussions took place, this format continued with all remaining interviews.

Disclosure of a priori knowledge (prompting) – It was anticipated that the interviewees would expect that I had some knowledge of the drugs under discussion and this was indeed the case. The literature-derived timelines were not shown to respondents. Instead, they just had access to the unannotated diffusion curve and therefore I was conscious to keep prompts to an absolute minimum to avoid cross contamination of respondents' accounts with the knowledge I had previously gained. While this would have inevitably been a limitation to be aware of in the minority of interviews where prompts were employed, the use of prompts where needed did stimulate further discussions and therefore were felt to be justified.

Official line responses – There were fewer occasions than expected of 'official line' stances during the interviews, and the pre-emptive measures regarding question design and prompting techniques referred to in the methods section provided an effective means of exploring beyond them if they did occur. Where respondents had been guarded during the main body of the interview, on reaching its conclusion it was not unusual for them to continue for a further 20 to 30 minutes, returning and elaborating on limited responses provided to earlier questions. This often yielded very rich data, as it was provided in a more relaxed context, as respondents were aware of the boundaries of the research and safe in the knowledge that I was not going to ask them further questions they were uncomfortable with or unable to answer.

Competitor discussions – Discussions surrounding competitor drugs were sometimes more revealing than anticipated as respondents were often more comfortable discussing other companies' strategies than their own.

Critical incidents (best/worst scenarios) – Explorations of situations that had not gone as well as expected were particularly useful for obtaining more detailed responses. By positioning this question towards the end of the interview, where an element of trust had been established, the interviewees tended to be more relaxed and open in their responses, often referring back to examples discussed during the main part of the interview, but in more depth.

Probing – Pricing was initially a category for discussion on the interview schedule. However, following the first two interviews, it became apparent that addressing pricing issues directly was sensitive for commercial reasons, and a subject that participants were not prepared to elaborate on. In order to maintain rapport, the decision was made not to raise this topic specifically in subsequent interviews, but to pursue it if the subject was raised by participants themselves. Some researchers of elites have stated that they often felt they were deferential and over-gracious (Duke, 2002), and on reflection I could have been more confrontational and challenging in the interviews. This was tempered however, by the risk that probing too far could have jeopardised chances of any future interviews and gaining access not only to other people within the company, but to others within the field.

Analysis

Sensitive nature of interview material – While respondents were advised that the interview material would be attributable to their company, I was conscious of the fact it should not be identifiable to individuals. Without respondent validation, I was perhaps more sensitive to the potential contentious nature with which this material could be viewed and therefore in situations where I had a selection of quotes to exemplify a theme I would preferentially use less contentious quotes or redact certain content, such as individual names within a quote.

Thematic analysis – De-contextualisation of quotes from the individual drug stories, followed by re-contextualisation within generic themes inevitably resulted in data fragmentation. This induced a risk within the analysis that an interpretation may not necessarily be clear to a reader, as part of the story to explain that quote may be entwined in a quote elsewhere (I, however, had knowledge of the case study in its entirety). Themes were also at risk of amalgamation or repetition due to linkages that developed between themes. I likened the experience of thematic analysis to a shuffle puzzle analogy. Where in the case of the puzzle, a picture or number sequence is divided into a grid of squares (with one missing so they can be shuffled around), in thematic analysis the quotes represent the squares, charting to form parts of the picture, but then having to be reorganised repeatedly to eventually obtain the complete picture. The difficulty is that unlike the puzzle, the analyst is not aware of what the final picture should resemble.

Reinterpretation – Mauthner *et al.* (1998), described how over time, through increasing knowledge and experience, original interpretations often shift when previously collected data is revisited. This was exacerbated by being a single analyst on this project as the lenses through which I viewed the data changed over the years I was conducting the analysis. This limitation could not be avoided, but its impact was lessened with transparency measures adopted in the analysis and through supervisory peer debriefing.

Triangulation

During the interviews, respondents had access to their diffusion curve to stimulate discussions, but they were not provided with the timeline information, so as to not influence their accounts. However, there is the need for consideration of potential cross contamination of the data sources at the triangulation stage. The possibility that the knowledge I gained from generating the timelines could have influenced my interpretation of the Industry accounts is a limitation. But one might argue that this is not contamination, so much as additional analysis.

3.8.3. Transferability (generalisability)

As discussed in section 3.2.1, generalisability in qualitative research is not assessed on the same criteria as quantitative research. The onus is on the reader to use the information provided in the analysis to consider the degree to which insights are likely to be transferable to other settings.

Sample – The value of qualitative research is not that this study represents in any statistical way the views of the whole pharmaceutical industry or their behaviour, but

that is has been able to generate new concepts and insights into the beliefs of an under-researched group around the issue of diffusion. In this study, participant numbers were particularly constrained by the access process, including issues around diminishing corporate memory within current personnel of the brands involved (particularly if the drug had lost patent protection), the need for access to senior personnel and a limited pool of companies to involve as a result of company mergers. This coupled with the time consuming nature of interviewing, transcribing and analysis meant that the sample was small, but not inconsistent with other interview-based pharmaceutical industry research. Despite this, saturation of response was achieved within the sample obtained.

The case study sample was diverse, covering various medical specialties; care settings (primary and secondary); political priorities; symptom and non-symptom based and life-saving/lifestyle conditions. All four case studies brought something different to the discussion, which enabled a broad set of diffusion issues to be elicited. Four similar cases would not have achieved the same depth of variation.

Provision of detailed context – Providing accounts of the context, methods used and examples of the raw data allows the reader to consider the researcher's interpretations and develop alternative interpretations based on their own context. Detailed descriptions of the case study drugs are provided in Chapter 4 and Appendices 13 to 16 (Case specific background sections). Characteristics of the type of pharmaceutical companies, together with individual descriptions of the companies involved are provided in Appendix 17. Detailed descriptions of the methods used, the types of respondents who participated, transparency measures regarding the analytical process and provision of raw data all contribute to enabling the reader to make their own judgement as to the

relevance (or transferability) of the conceptual research findings to their own contextual setting (Green, 1999).

Industry definition – The pharmaceutical industry is not just one organisation. While they all share a common purpose to manufacture, supply and market medicines, each of the different business models that exist will hold different beliefs around what affects the diffusion of pharmaceuticals based on their own individual challenges. This study involved representatives from only the major R&D pharmaceutical companies, and only from marketing and managerial personnel from within those companies. This presents a limitation with regard to how the dataset is interpreted. It is representing only a narrow perspective from a specific subsector of the pharmaceutical industry that will not necessarily be held by different types of company, or indeed by other professional groups within the same company.

It was not intentional to represent companies only from 'Big Pharma', but this was a consequence of the choice of case study drugs selected through the expert consultation exercise. While it is recognised as a limitation that only a narrow perspective is presented, 'Big Pharma' are worthy of researching in the first instance, as they are influential in setting agendas in the health care environment in the UK. Within the sample of 'Big Pharma' companies, variation did exist in terms of their size and available resources. Unless a conscious decision is made to purposively select cases from a range of different types of manufacturer, it is inevitable that in taking this approach to case study selection, the suggested cases were going to originate from within the 'Big Pharma' category of manufactures. The experts' selection was most likely influenced by what Rogers (1995) describes as pro-innovation bias, that suggests

only successful case studies are ever researched. In adopting a drug class approach to the case studies however, it provided an opportunity to research a range of drugs less successful than the market leader, albeit the order with which they were chosen was influenced by their market hierarchy position. It is acknowledged therefore that inferences of the findings of this research to other types of pharmaceutical company cannot be assumed. The research intends only to provide an insight into some of the beliefs of this particular group of stakeholders, which can be built on by other researches in the future to provide a much deeper understanding of this group as a whole.

Respondent bias – Respondents were self-selected by the companies involved and were of various levels of seniority within the marketing and market access departments, or senior management. Other groups within these companies, such as pharmacologists and clinicians would most likely have held different perspectives to those interviewed, but as the research project focussed on diffusion issues, it prompted the selection by the company of individuals who had experience with the drug at launch, or in the post-launch period. Responses were based on individual perceptions, subject to memory recall bias and not necessarily representative of their companies' views, or that of the Industry as a whole. Few participants had complete experience with the drug over its entire lifecycle and instead they tended to focus on specific areas of the curve they had direct knowledge of. Interviewees had comprehensive brand history knowledge and had often consulted with colleagues regarding explanations for past events on the diffusion curve, but ultimately these were second-hand accounts that could not be elaborated upon through probing. The fact that the research subthemes were aggregated and

conceptualised at a general level does mean however, that the broad headings would most likely feature amongst different groups of Industry individuals.

3.9. Chapter comment

This chapter has outlined the quantitative and qualitative methods employed to achieve three data sources that provide separate accounts of the same story: i) the diffusion curve based on usage data; ii) the timeline based on published literature and augmented by clinical expert opinion and iii) the pharmaceutical company drug-specific accounts for four case study drug classes: atypical antipsychotics for schizophrenia; bisphosphonates for postmenopausal osteoporosis; PDE5 inhibitors for erectile dysfunction and statins for the prevention of first and recurrent cardiovascular events. The Industry accounts were then analysed thematically across case studies using the Framework approach to thematic analysis to generate a synthesis of Industry-derived generic themes they perceive to be important in the diffusion of pharmaceuticals. The criteria used to assess the quality of the methods outlining the strengths and limitations of the approaches used have also been discussed.

CHAPTER 4

CASE STUDY RESULTS: DIFFUSION CURVES AND TIMELINES

4.1. Introduction

The following chapter presents the results of the four individual case studies, comprising the drug diffusion curves and timelines of key lifecycle events that affected each class. These sources not only provided background information ahead of the Industry interviews, but served as triangulation sources against which the Industry accounts could be later compared. While respondents were shown their individual diffusion curves, they did not have access to the timelines. For confidentiality reasons the individual company drug-specific accounts provided by respondents are not presented in the thesis. They were however used as a data source for case specific triangulation in Chapter 6, and their content, while not presented chronologically as a narrative, is conveyed thematically across case studies in the qualitative analysis that follows this chapter.

For each of the four case studies, further detail regarding background information on the disease, diagnostic criteria, clinical setting, drug pharmacology, dosage and administration protocols, regulation, safety, efficacy, cost, clinical guidelines and policy are outlined in Appendices 13 to 16. Profiles of the participant companies, including details of UK revenues of the case study drugs discussed are outlined in Appendix 17.

4.2. Case Study 1: Bisphosphonates for Postmenopausal Osteoporosis (PMO)

Bisphosphonates (BPs) are drugs used to increase bone mass in a variety of diseases of excessive bone loss including osteoporosis, Paget's disease, hypocalcaemia, osteolytic lesions and bone pain associated with malignancy. BPs were initially developed as detergents for use in hard water areas by Procter &Gamble in the early 1960s due to their high affinity for calcium and magnesium ions. By the late 1960s, their potential health benefits on calcified tissues started to become apparent. Disodium etidronate, the first BP, was initially used in dental products, but as it did not dissolve hydroxyapatite in the form of tartar and tooth enamel, its potential to prevent dissolution of bone (which is primarily hydroxyapatite in a cartilage matrix) made it a candidate as a treatment for diseases of bone loss.

Osteoporosis

Osteoporosis is a progressive systemic skeletal disorder characterised by low bone mass and micro-architectural deterioration of bone tissue. In adults, bone resorption by osteoclasts is closely coupled with bone formation by osteoblasts to maintain a state of equilibrium until around the age of 30, after which bone density starts to slowly decline. At menopause, oestrogen deficiency accelerates the activity of oseteoclasts. Consequently the net rate of bone resorption exceeds the rate of bone formation. The progressive decrease in bone mass leads to an increased susceptibility to fractures after minimal trauma or even normal load (WHO, 1994). BPs increase bone mineral density (BMD) by inhibiting osteoclast activity. They are indicated for both the treatment and prevention of osteoporosis (Table 4.1).

Table 4.1: Definitions of treatment and prevention in osteoporosis

	Definition
Treatment	Reduction in fracture risk in postmenopausal women *with osteoporosis* (BMD < -2.5), with or without a previous fracture to prevent further fracture.
Prevention	Prevention of bone loss in postmenopausal women *with osteopaenia* (BMD between -1 and -2.5) and increased risk of fracture to prevent osteoporosis from developing.

The class consists of eight drugs: alendronic acid (alendronate), disodium etidronate (etidronate), risedronate sodium (risedronate), zoledronic acid (zoledronate)[4], ibandronic acid (ibandronate)[4], disodium pamidronate (pamidronate)[5], sodium clodronate (clodronate)[5] and tiludronic acid (tiludronate)[5]. At the time of case study selection, only three BPs were licensed for osteoporosis (listed in Table 4.2). Interviews were conducted with MSD regarding alendronate and P&G for etidronate and risedronate.

Table 4.2: The bisphosphonate osteoporosis market

Drug	Brand name	Manufacturer	Market hierarchy	Market entry position	UK launch
Alendronate	Fosamax	MSD	1	2nd	Sep 1995
Risedronate	Actonel	P&G	2	3rd	May 2000
Cyclical Etidronate	Didronel PMO	P&G	3	1st	Nov 1991

BPs require complicated administration protocols, both as a result of their poor absorption from the gut and their potential to cause local irritation of the upper gastrointestinal mucosa (associated with the nitrogen-containing BPs alendronate and risedronate). Alendronate and risedronate have to be taken with 200mls and 120mls of water, respectively, and patients must remain upright for stipulated periods of time to

[4] Ibandronic acid and zoledronic acid were not licensed for osteoporosis in the UK until September 2005 and October 2007, respectively (insufficient data would have been available to pursue as case study drugs).
[5] Not licensed for osteoporosis.

avoid corrosive effects. To enhance absorption, patients cannot eat or drink before and immediately after administration (particularly products containing calcium).

Figure 4.1 shows the diffusion curves for the BP class[6]. Figure 4.2 shows the literature and expert augmented timelines for etidronate, alendronate and risedronate to provide potential explanations for the upward and downward trajectories depicted in the diffusion curves. The timeline is separated according to primary research events (key empirical clinical trials), secondary evidence and policy (meta-analyses, systematic reviews, clinical guidelines and government policies), and safety and regulatory events (with publication dates also provided). Commentaries of the events represented in each timeline are presented in Tables 4.3 to 4.5.

[6] Data is not indication-specific, however the majority of BP prescriptions are for osteoporosis (prevalence of Paget's disease is 5% in people over 55 years and only etidronate and risedronate are licensed for this indication). Despite a potentially high prevalence, corticosteroid-induced osteoporosis is not widely treated, therefore the curve predominantly represents use in postmenopausal osteoporosis.

Figure 4.1: Bisphosphonates - Diffusion Curves

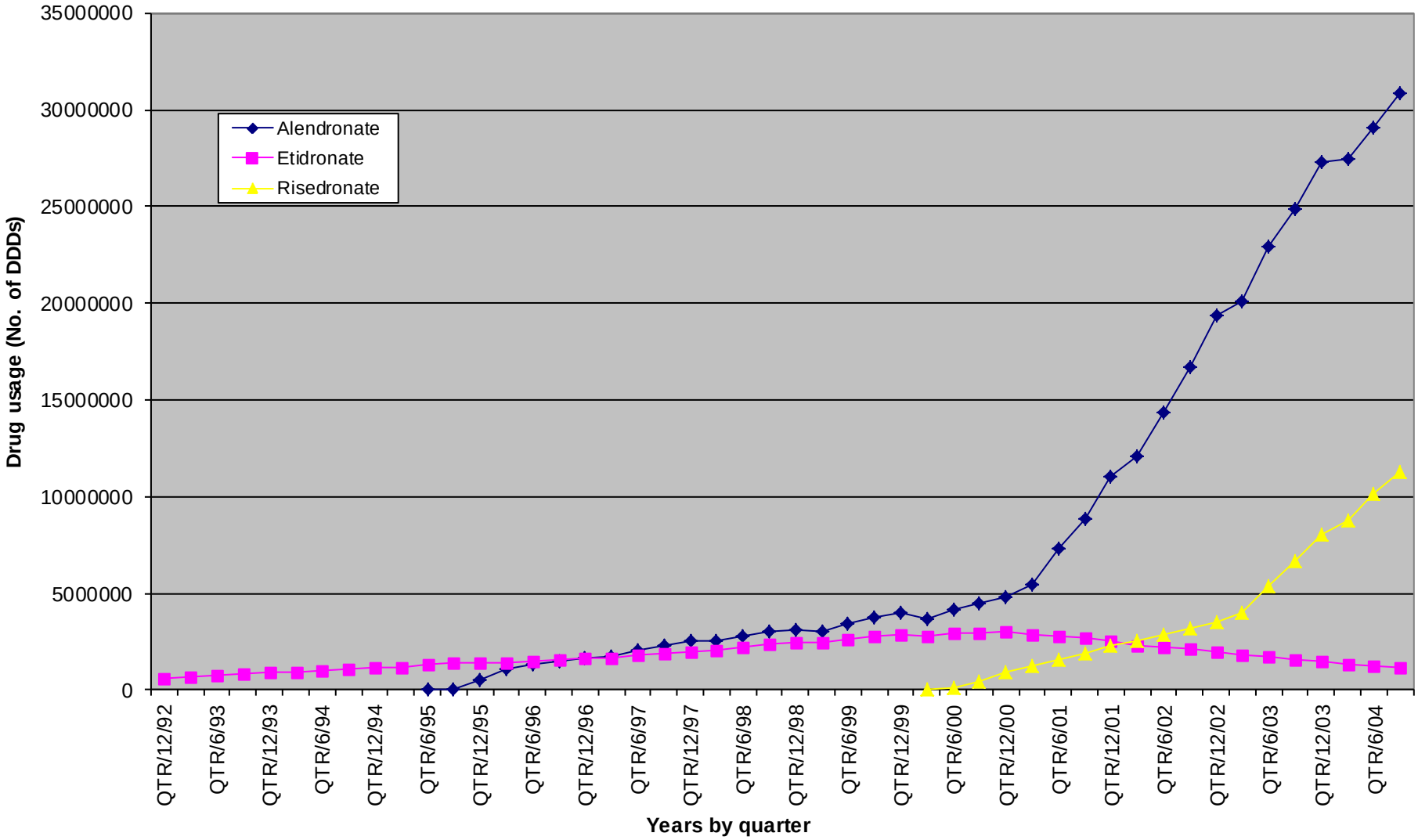
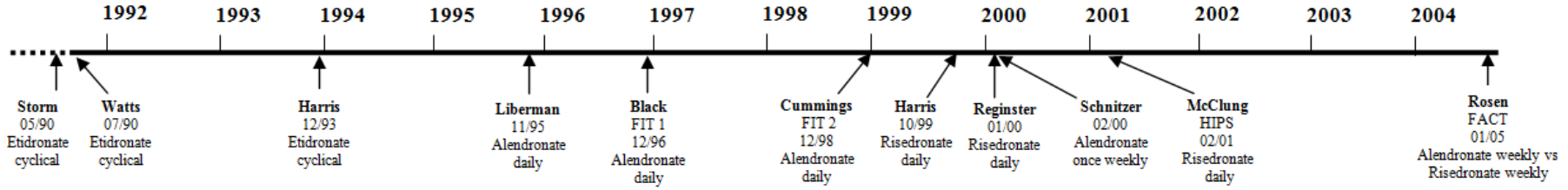
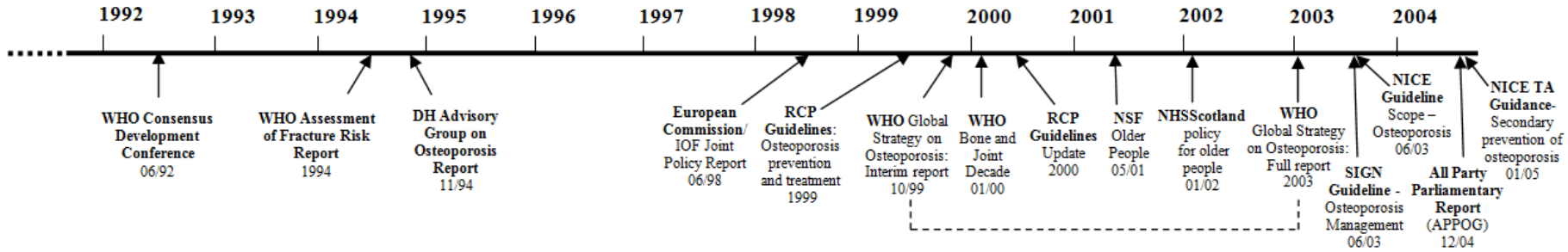


Figure 4.2: Bisphosphonates - Timeline of Literature and Expert-derived Diffusion Factors

<u>Primary</u> – Research Trials (See Table 4.3 for commentary)



<u>Secondary</u> – Guidelines/Reviews/Policy (See Table 4.4 for commentary)



<u>Regulatory/ Licensing (UK)</u> (See Table 4.5 for commentary)

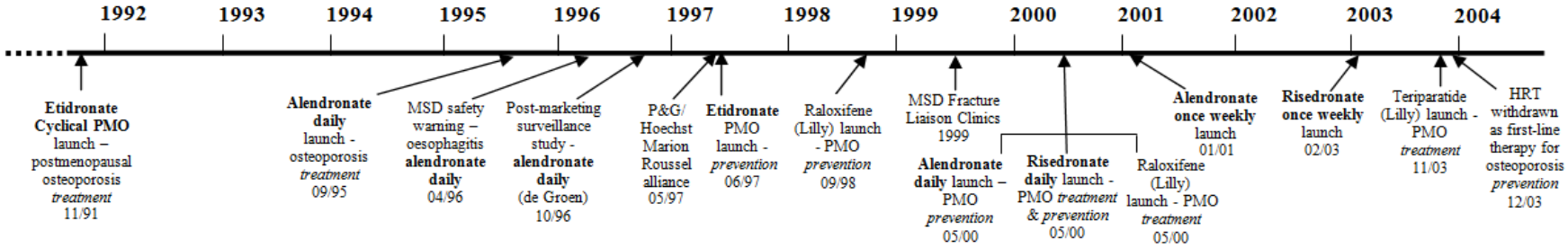


Table 4.3: Bisphosphonates - Timeline Commentary for Primary Level Evidence

Evidence summary: In women with established osteoporosis, alendronate, risedronate and etidronate are all effective in preventing vertebral fractures. Alendronate and risedronate also reduce the incidence of hip fractures. The evidence for this class of drugs however, is difficult to interpret for a variety of reasons (further detail provided in Appendix 13):

- Clinical trials in osteoporosis can investigate a) an increase in BMD or b) a reduction in the rate of new fractures. Fracture reduction is the clinically relevant end point, while an increase in BMD is considered a surrogate marker for fracture reduction, but this correlation is still uncertain.
- Results are complicated by subgroup analyses, loss of treatment arms due to ineffective dose ranging, data pooling and high rates of patient drop-outs.
- Relative risk reductions are often presented when the actual risk reductions are small.
- Due to the lengthy timescales involved to demonstrate comparative effectiveness on clinical endpoints, the majority of trials were placebo-controlled. Only one head to head comparison trial was published at the time when the interviews took place, the results of which were viewed with some scepticism due to the use of surrogate endpoints.

Trial	Study drugs[7]	Importance	Study design	Outcome
Storm *et al.*, 1990 (NEJM)	Cyclical etidronate vs placebo.	First randomised controlled trial in BPs to demonstrate increase in vertebral BMD.	**Treatment:** Randomised, double-blind placebo-controlled trial in 66 women with PMO over 3 years. Patients had between 1 and 4 vertebral compression fractures at baseline plus radiographic evidence of osteopaenia. Etidronate given cyclically - 400mg daily for 14 days followed by calcium 500mg daily for remainder of the 90 day cycle.	**Vertebral fracture reduction** (n=40 competed study) [8] Significant reduction in fracture rate between etidronate and placebo groups from week 60 to week 150; (6 vs 54 fractures per 100 patient years). **BMD:** Vertebral: significant increase in BMD of 5.3% etidronate vs -2.7% placebo (mean difference (MD)=8%). Non-vertebral: changes not significant at the forearm. No significant adverse events were identified.

[7] All women (placebo and intervention groups) with a calcium intake of less than 1000mg/day were also given supplemental calcium (range: 500-1000mg) and vitamin D (range 250-500 IU). Effects were therefore in addition to any benefit attributable to supplementation.

[8] Etidronate studies were powered to detect increments in BMD rather than fracture reduction, hence they only involved small numbers of patients compared with alendronate and risedronate studies.

Trial	Study drugs[7]	Importance	Study design	Outcome
Watts *et al*., 1990 (NEJM)	Cyclical etidronate vs placebo.	Largest ever study conducted on osteoporosis at that time.	**Treatment:** Randomised, double-blind placebo-controlled trial in 429 women with PMO over 2 years. Patients had between 1 and 4 vertebral compression fractures at baseline plus radiographic evidence of osteopaenia. Etidronate given cyclically - 400mg daily for 14 days followed by calcium 500mg daily for remainder of the 90 day cycle.	**Vertebral fracture reduction** (n=363 completed study): Rate of new vertebral fractures significantly reduced in the combined etidronate-containing arms by 50% vs placebo (29.5 vs 62.9 fractures per 1,000 patient years). **BMD:** Vertebral: significant increase of 4.2% and 5.2% in the two etidronate-containing arms of the study vs baseline. These changes were significantly different from placebo (approx 1.3%: exact value not presented. MD=approx 3-4%). Non-vertebral: changes were not significant at the hip and wrist. No significant adverse events were identified.
Harris *et al*., 1993 (Am J Med)	Cyclical etidronate vs placebo.	Extension study of Watts *et al*. (1990) - first to show an effect on non-vertebral BMD (hip sites).	One year extension study in 357 women with PMO (remaining study details as described in Watts *et al*., 1990).	Etidronate caused a significant increase in BMD at all hip sites vs placebo: femoral neck (1.44% etidronate vs -0.60% placebo: MD=2.0%); greater trochanter (2.65% vs -0.07%: MD=2.72%); Ward's triangle (2.14 vs -1.90: MD=4.0%). No significant adverse events were identified.
Liberman *et al*., 1995 (NEJM)	Alendronate daily vs placebo.	First major study of alendronate; first BP study powered to detect fracture reduction. Trial incorporated patients with osteoporosis according to the new WHO definition based on BMD T-score).	**Treatment:** Randomised, double-blind placebo-controlled trial in 994 women with PMO (defined as low BMD at the lumbar spine (T Score <-2.5), with or without fractures) over 3 years. Alendronate given as 5mg or 10mg daily for 3 years or 20mg for 2 years followed by 5mg for 1 year.	**Vertebral fracture reduction** (n=881 completed study): Treatment with alendronate reduced the incidence of new vertebral fracture by 48% vs placebo (3.2% vs 6.2%), decreased progression of vertebral deformities (33% vs 41%), and reduced loss of height (all significant). Study not sufficiently powered to demonstrate a significant effect on non-vertebral fractures. **BMD:** Only mean differences between alendronate and placebo groups presented (not actual values). BMD increased significantly at all sites in all 3 alendronate groups vs significant losses at all sites in the placebo group. Vertebral: MD=8.8%. Non-vertebral: femoral neck MD=5.9%; trochanter MD=7.9%; total body MD=2.5%. No significant adverse events were identified. Presented at the 77th Annual Meeting of the Endocrine Society, June 1995 (5 months before publication).
Black *et al*., 1996 **F**racture **I**ntervention **T**rial **(FIT 1):** **-** vertebral fracture arm • *with* baseline vertebral fractures (Lancet)	Alendronate daily vs placebo.	First mega-trial in osteoporosis. First study to demonstrate a reduction in incidence of non-vertebral (hip) fractures.	**Treatment:** Randomised, double-blind, placebo-controlled trial in 2,027 women with PMO (defined as low bone mass and at least 1 vertebral compression fracture at baseline) over 3 years. Alendronate given daily as 5mg for 2 years and 10mg daily for a further year. Study ended prematurely after 2 years due to benefit in treated patients.	**Fracture reduction** (n=1,946 completed study): Vertebral: incidence of radiographically defined fractures significantly reduced by 47% (8.0% vs placebo 15.0%) and clinically recognised fractures by 55% (2.3% vs placebo 5.0%). Non-vertebral: significantly reduced hip fractures (femoral neck) by 51% (1.1% vs placebo 2.2%), and wrist fractures by 48% (2.2% vs placebo 4.1%). Risk of any clinical fracture (secondary endpoint) significantly reduced by 28% (13.6% vs placebo 18.2%). **BMD** (only MDs and not actual values between alendronate and placebo groups were presented. Vertebral: Significant increase at lumbar spine (6.2%); lateral spine (6.8%). Non-vertebral: significant increases at femoral neck (4.1%); total hip (4.7%); trochanter (6.1%); whole body (1.8%); proximal forearm (1.6%). No significant adverse events, including upper GI side effects such as oesophagitis were identified. (Presented at the World Congress on Osteoporosis, Amsterdam 18-23 May 1996, 7 months before publication). Trial design published in May 1993 (Black *et al.*, 1993).

Trial	Study drugs[7]	Importance	Study design	Outcome
Cummings *et al*., 1998 (FIT 2): - clinical fracture arm • *without* baseline vertebral fractures (JAMA)	Alendronate daily vs placebo.	First major prevention study.	**Prevention and treatment:** Randomised, double-blind, placebo-controlled trial in 4,432 women with PMO and low femoral neck BMD but no vertebral fractures at baseline over 4 years. Most patients were osteopaenic (preventative component), but 37% had T-Score of <-2.5 which defined them as osteoporotic. Alendronate given daily as 5mg daily for 2 years and 10mg for remainder of 4 year trial.	**Fracture reduction** (n=4,272 completed study): Any clinical fracture (includes vertebral and non-vertebral): Reduction was non-significant (312 placebo vs 272 in the alendronate; 14%). None of the reductions were significant at the non-vertebral sites. This reduction was significant however, in the subgroup of women with osteoporosis (T-score <-2.5) =36% reduction. Vertebral: Alendronate significantly reduced the overall risk of developing a new radiographic vertebral fracture by 44% (2.1% alendronate vs 3.8% placebo). **BMD:** Significant increases at all three sites with alendronate vs placebo. Vertebral: lumbar spine (8.3% alendronate vs 1.5 % placebo: MD=6.8%). Non-vertebral: femoral neck (3.8% vs -0.8%: MD=4.6%); total hip (3.4% vs -1.6%: MD=5%). No significant adverse events were identified.
Harris *et al*., 1999 (JAMA)	Risedronate daily vs placebo.	First large scale study in risedronate.	**Treatment** Randomised, double-blind, placebo-controlled trial in 2,458 women with PMO (at least 1 vertebral fracture at baseline) over 3 years. Risedronate given daily (2.5mg or 5mg). 2.5mg arm discontinued after 1 year (remaining groups n=1,628).	**Fracture reduction** (n = 939 completed study): Vertebral: Risedronate significantly reduced the cumulative incidence of new vertebral fracture by 41% vs placebo (11.3% risedronate vs 16.3% placebo). Non-vertebral (wrist, hip and/or pelvis, humerus, leg, clavicle): significant cumulative reduction of 39% (5.2% risedronate vs 8.4% placebo). **BMD:** Vertebral: significant mean increase at lumbar spine (5.4% risedronate vs 1.1 % placebo: MD=4.3%). Non-vertebral: significant mean increase at femoral neck (1.6% vs -1.2%: MD=2.8%); femoral trochanter (3.3% vs -0.7%: MD=4%); midshaft of the radius (0.2% vs -1.4%: MD=1.6%). No significant adverse events were identified.
Reginster *et al*., 2000 (Osteoporosis Intl)	Risedronate daily vs placebo.	Study demonstrated a non-significant reduction in non-vertebral fracture in contrast to Harris *et al*., 1999.	**Treatment:** Randomised, double-blind, placebo-controlled trial in 1,226 women with PMO (at least 2 prevalent vertebral fractures at baseline) over 3 years. Risedronate given daily (2.5mg or 5mg). 2.5mg arm discontinued after 2 years (remaining groups n=814).	**Fracture reduction** (n=472 completed study): Vertebral: Risedronate (5mg) significantly reduced incidence of new vertebral fracture by 49% vs placebo (18% risedronate vs 29% placebo). Non-vertebral (wrist, humerus, hip, pelvis, leg, clavicle): reduction was non-significant (10.9% risedronate vs 16% placebo: 33% relative risk reduction). **BMD:** Only mean differences between risedronate and placebo groups presented (not actual values) Vertebral: significant increase at spine (MD=5.9%). Non-vertebral: significant increases at femoral trochanter (MD=6.4%); femoral neck (MD=3.1%); midshaft radius (MD=2.1%). No significant adverse events were identified.
Schnitzer *et al*., 2000 (Aging Clin Exp Res)	Alendronate 10mg daily vs alendronate 70mg once weekly.	Key study to demonstrate equivalent efficacy of a once weekly formulation.	**Treatment** Double-blind therapeutic equivalence trial comparing alendronate 70mg once weekly with alendronate 10mg daily in 889 women with PMO (defined as BMD T-score at the lumbar spine or femoral neck of <-2.5, or prior vertebral or hip fracture) over 1 year.	Changes in BMD and biochemical markers of bone turnover were equivalent across all treatment groups. **BMD:** Vertebral: mean increase at lumbar spine (5.1% once weekly vs 5.4% 10mg daily - both significant from baseline). Non-vertebral: mean increase at femoral neck: 2.3% once weekly vs 2.9% 10mg daily; total hip: 2.9% vs 3.1%; trochanter: 3.9% vs 4.4%; total body: both 1% (all significant from baseline).

Trial	Study drugs[7]	Importance	Study design	Outcome
McClung *et al*., 2001 **H**ip **I**ntervention **P**rogramme **S**tudy **(HIPS)** (NEJM)	Risedronate daily vs placebo.	Intended to be the first study powered to show effect of BPs on hip fracture. Beaten to it by FIT 1 that was fortuitously able to demonstrate impact on hip at earlier stage.	**Treatment:** Randomised, double-blind, placebo-controlled trial over 3 years in: **Arm1** (n=5,445): women 70-79 years with osteoporosis (T-score at femoral neck of -4; or <-3 plus a non-skeletal risk factor for hip fracture (poor gait or propensity to fall); **Arm 2** (n=3,886): women ≥80 years selected primarily on basis of non-skeletal risk factors (with ≥1 clinical risk factor for hip fracture, or low BMD (T-score <-4; or <-3 plus hip axis length of 11.1cm or greater) – only 16% recruited on low BMD at femoral neck. Majority (58%) were recruited solely on basis of clinical risk factor e.g. fall-related injury. Risedronate given daily (2.5mg or 5mg).	**Fracture reduction** (n=5,100 completed study): Non-vertebral (hip): Risedronate significantly reduced risk of hip fracture among elderly women with confirmed osteoporosis, but not among elderly women selected primarily on basis of risk factors other than low BMD. **Arm 1:** hip fracture incidence significantly reduced by 40% (1.9% vs 3.2% placebo). Effects of both risedronate doses were similar. **Arm 2:** hip fracture incidence reduction was non-significant (4.2% vs 5.1% placebo: 20% reduction). Among **all** women assigned risedronate, hip fracture incidence was significantly reduced by 30% vs placebo (2.8% vs 3.9%). No significant adverse events were identified.
Rosen *et al*., 2005 **F**osamax **A**ctonel **C**omparison **T**rial **(FACT)** (J Bone Miner Res)	Alendronate once weekly vs Risedronate once weekly.	First head to head trial on a comparable basis – same formulation. Used surrogate marker as outcome measure.	**Treatment:** Randomised, double-blind, head to head trial in 1,053 women with PMO with low BMD (T-Score ≤-2.0 in at least one of four sites – not technically osteoporotic as none of the baseline BMDs were ≤-2.5 and only 12% had history of previous fracture after age 45). Alendronate (70mg) or risedronate (35mg) given weekly over 1 year.	**BMD:** (n=892 completed study): Both drugs produced significant increases in BMD after 6 and 12 months at all sites from baseline, but the increases with alendronate were significantly greater at all time points and at **all** skeletal sites. The use of BMD instead of fracture reduction however makes the outcome difficult to interpret. Vertebral: mean significant increase at lumbar spine: 3.7% alendronate vs 2.6% risedronate (MD=1.1%). Non-vertebral: mean significant increases at femoral trochanter: 3.4% alendronate vs 2.1% risedronate (MD=1.4%); total hip: 2.2% vs 1.2% (MD=1%); femoral neck: 1.6% vs 0.9% (MD=0.7%). **Markers of bone turnover:** Both drugs significantly reduced bone turnover, but the reductions were greater with alendronate. No significant differences found in upper GI tolerability between the two drugs. *(Presented at the 26th annual meeting of the American Society for Bone and Mineral Research Oct 2004 (3 months before publication).*

Table 4.4: Bisphosphonates - Timeline Commentary for Secondary Level Evidence and Policy

Secondary Evidence and Policy	Description
WHO Consensus Development Conference, 1992	The World Health Organization (WHO) in partnership with the International Osteoporosis Foundation (IOF) [9] organised the first official discussion by experts on redefining osteoporosis on the basis of low BMD.
WHO Assessment of Fracture Risk Report, 1994 (Technical Report Series 843)	The WHO redefined osteoporosis to reflect change in perception amongst clinical experts, recommending that diagnosis of osteoporosis be based on BMD T-scores (the number of standard deviations below the average peak BMD in young healthy adults), with the aim of identifying and treating individuals *at risk* before they developed fractures ('osteopaenia' was a term created to describe this pre-osteoporotic state). Osteoporosis changed from a tangible fracture-based disease, into one of risk, and in doing so expanded the eligible patient population. Controversy surrounded the WHO definition: i) correlation between low BMD and increased fracture risk was contentious – BMD needed to be considered within the context of other risk factors such as increasing age and propensity to fall ii) use of a surrogate marker conceptualised a risk factor as a disease iii) comparison with normal subjects of the same age and sex (Z-score) would have been a more appropriate measure.
DH Advisory Group on Osteoporosis report (Barlow, 1994)	Department of Health Advisory Group on Osteoporosis established by Health Minister Baroness Cumberlege in 1993 to produce a comprehensive review of the issues pertinent to improving the management of osteoporosis. The recommendations of the report published in 1994 were: (a) better coordination of services in osteoporosis management, (b) greater availability of bone densitometry facilities for defined clinical indications, (c) provision of these facilities at the discretion of purchasers at a local level, and (d) the development of guidelines for osteoporosis management through the Royal Colleges. Baroness Cumberlege accepted the recommendations of the report in January 1995 and drew attention to the proposal that bone densitometry should be available to assist clinical decision making for certain patients identified as being at high risk. The report led to the recommendation that guidelines on the prevention and treatment of osteoporosis be prepared under the auspices of the Royal College of Physicians (RCPs).
European Commission/IOF Joint Policy Report, 1998	Landmark publication 'Osteoporosis in the EC - Action for Prevention' resulting from a collaboration of the European Commission and IOF, which accelerated action on osteoporosis throughout Europe. The report outlined epidemiologic issues, provided an overview of bone physiology, information about the diagnosis and assessment of risk and contained eight recommendations for the prevention of fractures and for the management of patients with osteoporosis.
RCP Guidelines: Osteoporosis prevention and treatment, 1999	The Royal College of Physicians (RCP) guidelines recommended the use of BPs as one of several other treatments and lifestyle advice if osteoporosis is confirmed by DEXA scanning (T-score of <-2.5), or if osteopaenia is confirmed in the presence of previous fracture. Alendronate and risedronate however, were the only interventions with grade A recommendations across all sites in terms of anti-fracture efficacy (spine, non-vertebral and hip) and all three bisphosphonates were graded A in their effect on prevention/reduction of bone loss.
WHO Global Strategy on Osteoporosis - Interim report, (Genant *et al.*, 1999) - Full report (WHO 2003 Technical Report Series 921)	In recognising the global problem posed by osteoporosis, the WHO produced a global strategy for prevention and control of osteoporosis, focusing on three major functions: prevention, management and surveillance. Management included the bisphosphonates amongst other pharmacological interventions. A synopsis of the evidence to date was presented for etidronate, alendronate and risedronate, but with no specific recommendations as to which one should be used in preference..
WHO – Bone and Joint Decade (2000-2010), 2000	The Bone and Joint Decade was a global campaign to improve the quality of life for people with musculoskeletal conditions including osteoporosis. It was launched by the WHO on January 13th 2000 following endorsement by the United Nations in November 1999, and several nations including the UK. The aim was to advance the understanding and treatment of these conditions through increasing funding for research, raising awareness and promoting cost effective prevention and treatment measures.
RCP Guidelines Update, 2000	Royal College of Physicians reproduced guidelines to include an update on pharmacological interventions and an algorithm for management.
NSF for Older People, (DH, 2001a)	The National Service Framework (NSF) for Older people set out eight standards which aimed to provide person-centred care, remove age discrimination, promote older people's health and independence and to 'fit the services around people's needs'. Osteoporosis came under the remit of Standard 6: Falls. Its aim was to reduce the number of falls which result in serious injury and ensure effective treatment and rehabilitation for those who have fallen. However, reference to osteoporosis treatment

[9] The IOF is a a non-governmental foundation in Switzerland which represents a global alliance of patients, medical and research societies, scientists, health care professionals and health industry. Its remit is to increase awareness and improve prevention, early diagnosis and treatment of osteoporosis.

Secondary Evidence and Policy	Description
	was minimal and very general "Drug interventions, for example, hormone replacement therapy, selective oestrogen receptor modulators (SERMS) and bisphosphonates will be most cost effective when prescribed in carefully defined, high risk, older people."
NHS Scotland policy for older people, 2002	Scottish policy document 'Adding Life to Years: Report of the Expert Group on Healthcare of Older People' provided an overview and description of the major health problems of older people in NHS Scotland. Osteoporosis came under the subsection 'Falls and fracture prevention' in Chapter 4 which deals with the wider issue of an 'Overview of major health problems'. The document refers to the RCP guidelines, but also states that osteoporosis management should be an important part of any falls assessment.
SIGN Guideline No. 71 – Osteoporosis management, 2003	In the Scottish Intercollegiate Guidelines Network (SIGN) guidelines, all three BPs were recommended in women aged 60 and over with 2 or more vertebral fractures without the need for DEXA scanning. If patients have one vertebral fracture, BPs are only given if the BMD T-score is ≤-1.6 at the femoral neck or ≤-2 at the lumbar spine. In women with a non-vertebral fracture, alendronate and risedronate are recommended only if the BMD T-score is ≤-2.5 at the femoral neck or ≤-2 at the lumbar spine. In frail elderly women (aged 80+ years) with a diagnosis of osteoporosis, but with or without previous fracture, alendronate and risedronate are recommended.
NICE Guideline scope - osteoporosis, 2003	Guideline on the assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. The scope, published in June 2003 outlined that several pharmacological and non-pharmacological interventions that reduce the risk of fracture would be assessed in the guidelines. As the guideline however was to incorporate recommendations from the technology appraisals on the primary and secondary prevention of osteoporotic fragility fractures in postmenopausal women, it was put on hold for several years and was only published in August 2012.
NICE TA (Technology Appraisal) Guidance – secondary prevention of osteoporosis, 2005	Bisphosphonates were recommended as first-line treatment for the secondary prevention of osteoporotic fragility fractures in postmenopausal women (incorporated 16 RCTs for alendronate; 11 RCTs for etidronate; 7 RCTS for risedronate). There was however, no differentiation between which of the three bisphosphonates should be used preferentially. The selection of individuals for treatment was based on the inter-related risk factors of age and low BMD, and takes into account age-independent risk factors. The choice was to be based on clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients.
All Party Parliamentary Report (APPOG), 2004	The All Party Parliamentary Osteoporosis Group (APPOG) was established in response to concerns that the NHS would not meet Standard Six of the NSF for Older People. Although the inclusion of osteoporosis within the NSF was a clear indication of priority, the subsequent apparent lack of endorsement for osteoporosis from Government and the exclusion of the condition from the General Medical Services (GMS) contract undermined the position of osteoporosis within the NHS. The resulting report 'Falling Short' urged the Government to consider the inclusion of osteoporosis within the Quality and Outcomes Framework (QOF) of the GMS contract.

Table 4.5: Bisphosphonates - Timeline Commentary for Safety and Regulatory Events

Note: Not all licensing events that appear on the timeline are represented in the table below. Only those events that required additional context are presented.

Event	Description
Cyclical Etidronate launch Nov 1991	The first BP entered an osteoporosis market populated predominantly with hormone therapies (oestrogen and calcitonin), vitamins supplements and sodium fluoride. As the manufacturer of the first BP on the market for osteoporosis, P&G had a significant challenge to raise awareness of the condition amongst clinicians and patients and encourage consensus agreement in diagnosis and treatment of the disease. Cyclical administration in conjunction with calcium avoided osteomalacia ('soft bones' as a result of impaired mineralisation) that became apparent with its continuous use in Paget's disease.
Alendronate daily launch, Sep 1995	Alendronate's increased potency (up to 10,000 times greater than etidronate) meant that it could be given at low doses continuously without risk of osteomalacia This was anticipated to increase patient compliance compared with cyclical etidronate regimens.
MSD safety warning – oesophagitis (alendronate daily), Apr 1996	Ahead of publication of a post-marketing surveillance study, MSD released a 'Dear Dr' letter strengthening the importance of correct administration following concerns of oesophagitis. There was also a worldwide revision of the package insert for Fosamax (alendronate) to clarify the conditions of administration. The list of contraindications was also extended to include not only patients with active upper gastrointestinal problems, but those with abnormalities of the oesophagus which delay oesophageal emptying (stricture), or inability to sit/stand upright for at least 30 minutes.
Post-marketing surveillance study (alendronate daily) de Groen *et al.*,*Oct* 1996	Study published in the NEJM indicated the extent of the safety issues that had been reported with alendronate. In addition to the three cases of severe oesophagitis described, further analysis showed that between October 1995 and March 1996, from an estimated 475,000 prescriptions of alendronate, 1,213 reports of adverse effects had been received by MSD, of which 199 were related to the oesophagus. Symptoms were categorised as serious or severe in 51, and of these, 32 patients were hospitalised. The endoscopic findings generally indicated chemical oesophagitis, with erosions or ulcerations and exudative inflammation accompanied by thickening of the oesophageal wall. In the majority of cases however, the effects appeared to be due to incorrect administration; either taking with little or no water, lying down during or after ingestion, or continuing to take alendronate after the onset of symptoms.
P&G/Hoechst Marion Roussel alliance May 1997	In May 1997, P&G formed a global alliance with Hoechst Marion Roussel (now Sanofi-Aventis) to commercialise risedronate (Actonel) collaboratively in Europe, the United States and Canada. The role of the 'Alliance for Better Bone Health' was to promote disease awareness through numerous activities to support physicians and patients. This was in contrast to etidronate, which they launched independently.
Raloxifene and teriparatide launch (Lilly) Sep 1998 and Nov 2003, respectively	Raloxifene (a selective oestrogen receptor modulator) and teriparatide (parathyroid hormone), both drugs manufactured by Lilly, were competitors to the BPs. However NICE guidance in 2005 recommended that they should be reserved for use in patients in whom BPs are contraindicated, those who are intolerant, or those who have had an unsatisfactory response.
MSD fracture liaison clinics 1999	Few health authorities provided osteoporosis services in accordance with recommendations, particularly with regard to bone density (DEXA) scans. In response, MSD established Fracture Liaison Clinics with specialist nurse liaison to identify patients suitable for treatment.
Alendronate once weekly launch Jan 2001	The constraints of the complicated daily dosing regime prompted the development of a once weekly 70mg formulation of alendronate. It was regarded as a key breakthrough to improve compliance. Oesophageal turnover occurs in approximately 5 days, therefore a once weekly administration allowed time for regeneration of oesophageal mucosa between doses.
HRT withdrawn as first-line therapy for osteoporosis prevention Dec 2003	Two large studies reported that the balance of risks of using hormone replacement therapy (HRT) for this indication outweighed the benefits. This left this particular market open to other osteoporosis therapies.

4.3. Case Study 2: Atypical Antipsychotics for Schizophrenia

The atypical antipsychotics (AAs), or second generation antipsychotics, are not technically a class of drugs. Their only consistent feature is that they all act upon the dopamine D_2 receptors. It is the way in which they interact with other receptors that is responsible for the subtle differences in their side effect profiles. While their therapeutic effects are broadly comparable, structurally and mechanistically they are all very heterogeneous, which from a marketing perspective has provided the grounds on which to distinguish these products. AAs were hailed as a major advance, principally because of their lower propensity to cause extrapyramidal symptoms (EPS) and tardive dyskinesia (TD). These are particularly unpleasant neurological side effects, often considered by many patients worse than the disorder itself, that had plagued the conventional antipsychotics (CAs) since their introduction in the 1950s. While CAs are effective in treating the positive symptoms of schizophrenia, AAs additionally reduced the negative symptoms.

Schizophrenia

Schizophrenia is a mental illness characterised by a broad range of cognitive, emotional and behavioural problems. It is the result of alterations in brain chemistry, particularly over-activity of dopamine in certain regions of the brain. People with schizophrenia typically hear voices (auditory hallucinations) that often criticise or abuse them. Patients try to make sense of these hallucinations, which can lead to the development of strange beliefs or delusions.

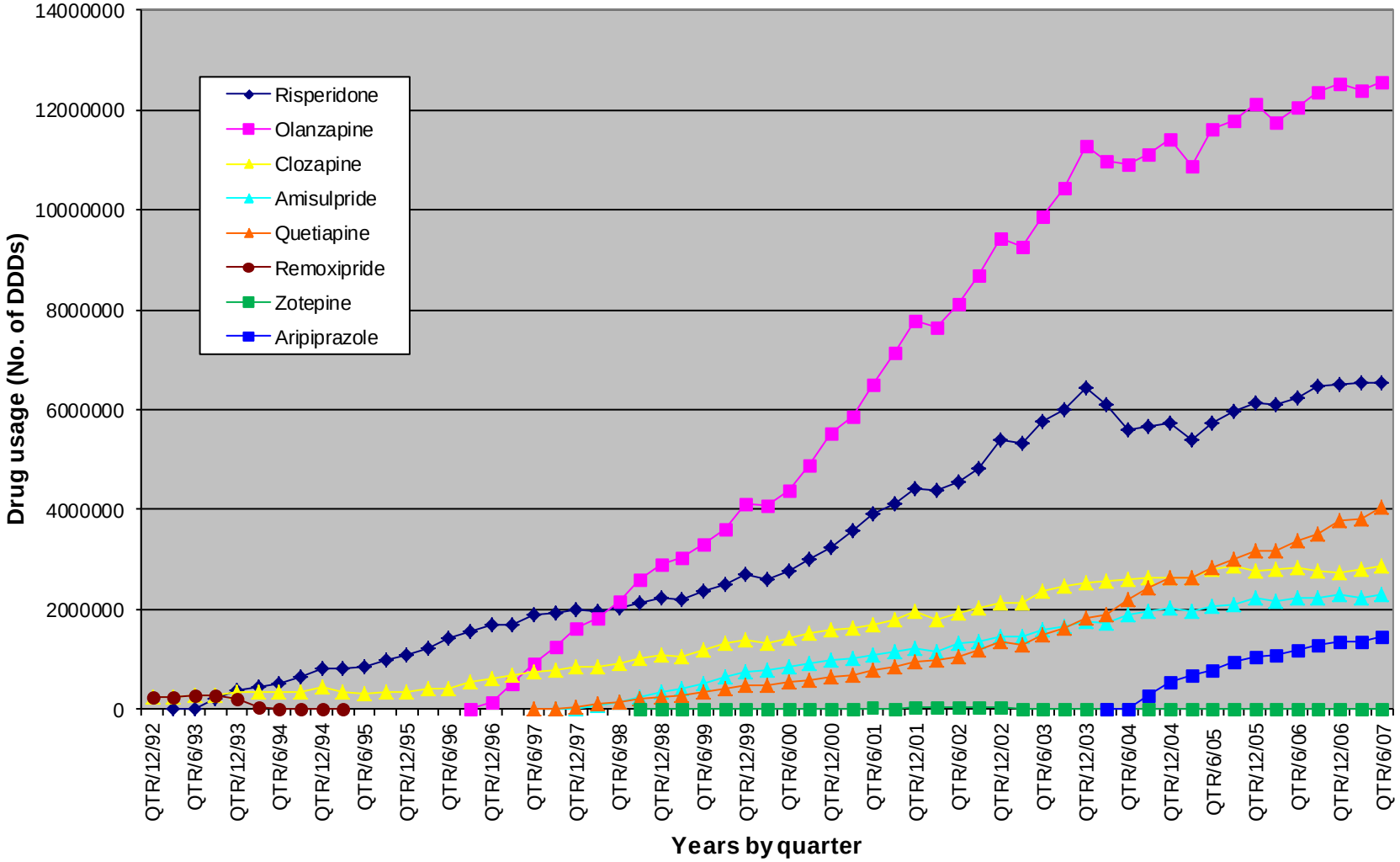
The class consists of nine drugs listed in Table 4.6. Interviews were conducted with Lilly, Janssen-Cilag and AstraZeneca for olanzapine, risperidone and quetiapine, respectively.

Table 4.6: The atypical antipsychotic schizophrenia market

Drug	Brand name	Manufacturer	Market hierarchy	Market entry position	UK launch
Olanzapine	Zyprexa	Eli Lilly (now Lilly)	1	5th	Oct 1996
Risperidone	Risperdal	Janssen-Cilag, Organon	2	3rd	Jun 1993
Clozapine	Clozaril	Novartis	3	1st	Jan 1990
Quetiapine	Seroquel	AstraZeneca	4	6th	Sep 1997
Amisulpride	Solian	Sanofi-Synthelabo (now Sanofi Aventis)	5	7th	Oct 1997
Remoxipride	Roxiam	AstraZeneca	6	2nd	May 1991 (withdrawn 1994)
Sertindole	Serdolect	Lundbeck	7	4th	Jul 1996 (withdrawn 1999)
Zotepine	Zoleptil	Orion	8	8th	Nov 1998
Aripiprazole	Abilify	Bristol-Myers Squibb	9	9th	Jun 2004

Figure 4.3 shows the diffusion curves for the AAs. Figure 4.4 shows the literature and expert augmented timelines for olanzapine, risperidone and quetiapine. Commentaries of the events represented in each timeline are presented in Tables 4.7 to 4.9.

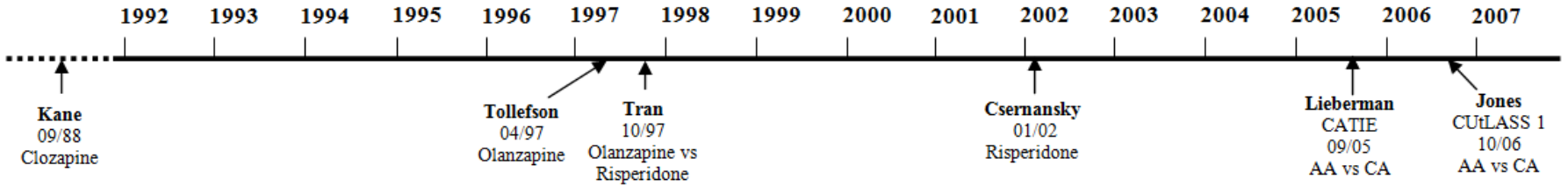
Figure 4.3: Atypical Antipsychotics - Diffusion Curves[10]



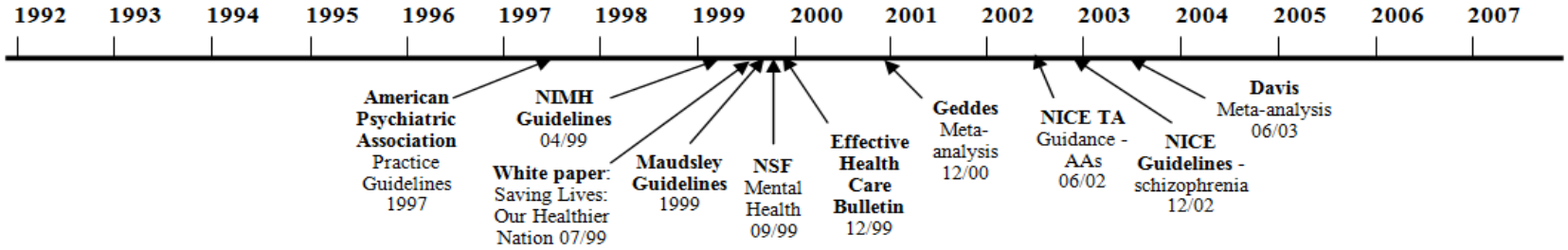
[10] The IMS Health dataset is not able to separate between schizophrenia and bipolar indications.

Figure 4.4: Atypical Antipsychotics - Timeline of Literature and Expert-derived Diffusion Factors

<u>Primary</u> – Research Trials (See Table 4.7 for commentary) **Key: AA = atypical antipsychotics; CA = conventional antipsychotics**



<u>Secondary</u> – Guidelines/Reviews/Policy (See Table 4.8 for commentary)



<u>Regulatory/ Licensing (UK)</u> (See Table 4.9 for commentary)

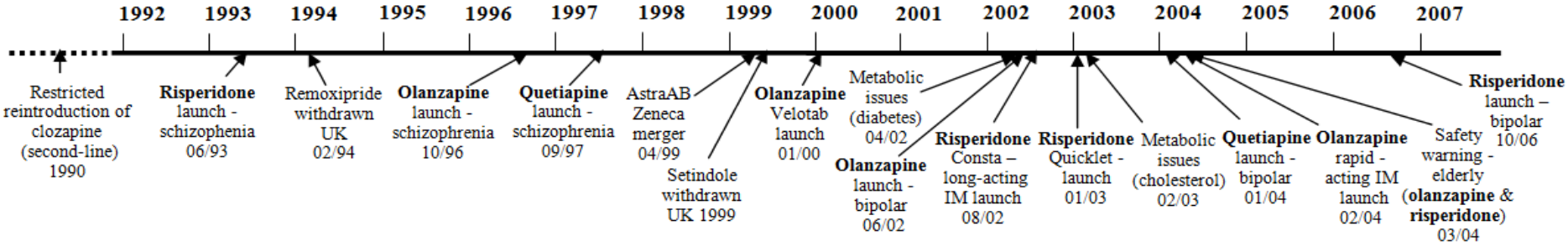


Table 4.7: Atypical Antipsychotics - Timeline Commentary for Primary Level Evidence

Evidence summary: The wealth of clinical evidence for this class of drugs is extensive. Several hundred randomised controlled trials (RCTs) and meta-analyses have been produced, either comparing AAs with placebo, with the CAs, or with each other in head to head trials. However, with the exception of clozapine (Wahlbeck *et al*., 1999; Jones *et al*., 2006), evidence of the superior efficacy and side effect profile of the other AAs has neither been consistent or robust (Leucht *et al*., 1999; Geddes *et al*., 2000; Davis *et al*., 2003; Leucht *et al*., 2003a; Leucht *et al*., 2003b). There is evidence suggesting AAs are associated with a lower risk of extrapyramidal symptoms (EPS) than CAs, and that fewer people stop treatment, however, with the metabolic risks of weight gain and diabetes, it is questionable whether they represent major gains in effectiveness or tolerability (Gardner *et al*., 2005). Clozapine and olanzapine are associated with more anticholinergic side effects and weight gain than the other atypicals, and risperidone with more prolactin elevation. Treatment decisions involve a trade-off between efficacy and acceptable side effects.

Trial	Study drugs[11]	Importance	Study design	Outcome
Kane *et al*., 1988	Clozapine vs chlorpromazine in people refractory to CAs (haloperidol).	Trial defined new class of atypical antipsychotics.	Randomised double-blind active-control trial in 268 patients over 6 weeks.	In patients unresponsive to CAs, approximately 30% of patients randomised to clozapine responded compared with 3% on chlorpromazine. An issue with the trial was that response to CAs had already been flushed out prior to randomisation, but it did demonstrate clozapine was acting somewhat differently. First trial to offer a new development in this field since the original MRC trial showing efficacy for the first generation antipsychotics.
Tollefson *et al*., 1997	Olanzapine vs haloperidol.	Largest ever study undertaken on a psychiatric population. Based on their prior experience with fluoxetine (Prozac), Lilly were aware of the need for much larger scale trials in psychiatry, and conducted a groundbreaking mega-trial for olanzapine. Most trials up to that point were recruiting between 200-300 patients.	Multicentre, randomised, double-blind, mega-trial in 1,996 patients over 6 weeks.	Significant improvement in negative symptoms, EPS, prolactin levels and response rate in the olanzapine group vs haloperidol and significantly fewer discontinuations of treatment (66.5% patients in olanzapine group vs 46.8% haloperidol group completed 6 weeks of treatment). A preview of the data was presented by Beasley (Lilly clinical research advisor and global physician for olanzapine) nearly a year before launch at the American College of Neuropsychopharmacology meeting in December 1995.
Tran *et al*., 1997	Olanzapine vs Risperidone.	First head to head trial.	Multicentre, randomised, double-blind, head to head trial in 339 patients over 28 weeks.	Olanzapine demonstrated significantly greater efficacy in negative symptoms and overall response rate vs risperidone. EPS, hyperprolactinaemia and sexual dysfunction significantly lower in olanzapine treated patients. Significantly fewer adverse events were reported in the olanzapine group. The size of these effects has since been questioned in systematic reviews and large scale trials.

[11] For this particular class of drugs, placebo-controlled trials are equally as important as head to head trials. Being able to demonstrate side effects as close to placebo as possible is the defining differentiating factor between the AAs.

Trial	Study drugs[11]	Importance	Study design	Outcome
Csernansky *et al*., 2002	Risperidone vs haloperidol.	First long-term trial. The need for a long-term trial was critical, as up to that point, trials were all short-term, usually of 6 weeks duration which is not reflective of chronic condition such as schizophrenia that can last up to 50 years.	Double-blind RCT in 397 patients for a minimum of 1 year.	Adult outpatients with clinically stable schizophrenia or schizoaffective disorder have a lower risk of relapse if they are treated with risperidone than with haloperidol.
Lieberman *et al*., 2005 **CATIE** **C**linical **A**ntipsychotic **T**rials of **I**ntervention **E**ffectiveness (US trial)	Olanzapine, quetiapine, risperidone ziprasidone vs CAs (perphenazine).	Large scale publicly funded comparator trial. Due to the conjecture regarding effectiveness of AAs vs CAs, the National Institute of Mental Health in the USA sponsored a large-scale independent trial.	Randomised, double-blind, active-control trial in 1,493 patients over 1 year.	No benefits of AAs over CAs. Patients discontinued all medications at a high rate (74% before 18 months and median time to discontinuation was 6 months), indicating substantial limitations in the effectiveness of the drugs. Olanzapine was marginally better in terms of clinical efficacy but was associated with greater weight gain and increases in measures of glucose and lipid metabolism. The slightly higher then recommended dose of olanzapine used could account for greater efficacy but worse side effects. Perphenazine was not only as effective as three of the four AAs, but also did not cause more EPS side effects. Perphenazine was chosen as the comparator to deal with equipoise issues i.e. it would not raise antibodies unlike chlorpromazine as it would not have ever been used before in these patients.
Jones *et al*., 2006 **CUtLASS 1** **C**ost **Ut**ility of the **L**atest **A**ntipsychotic Drugs in **S**chizophrenia **S**tudy (UK trial)	Amisulpride, olanzapine, quetiapine, risperidone vs CAs (mainly sulpride).	Publicly funded comparator trial to consider economic impact.	Multicentre, randomised active-control trial in 227 patients for 1 year.	No disadvantage across one year in terms of quality of life, symptoms or associated costs of care in using CAs rather than AAs.

Table 4.8: Atypical Antipsychotics - Timeline Commentary for Secondary Level Evidence and Policy

Secondary Evidence and Policy	Description
American Psychiatric Association Practice Guidelines, 1997	Major influence in prescribing practices in psychiatry in USA, with impact in the UK and Europe. Supported use of AAs as first-line treatment.
NIMH (National Institute of Mental Health) Guidelines (USA), Dawkins *et al*., 1999	Guidelines stated that atypicals merit first-line consideration in the domain of antipsychotic drugs. NIMH later funded the CATIE trial (2005) that demonstrated no apparent difference between AAs and CAs.
White paper. Saving Lives: Our Healthier Nation, (DH, 1999a)	A Government action plan to tackle poor health and improve the health of everyone. There was a particular focus on the main conditions responsible for death including mental illness. The pledge was to reduce the death rate from suicide and undetermined injury by at least a fifth.
Maudsley Prescribing Guidelines (UK), 1999	Leading clinical reference guidelines (regarded as an institution in the UK) for all practising mental health clinicians. Annual publication produced in-house by Maudsley Hospital, but 5th edition (1999) was the first publicly available edition, and therefore had the potential for wider impact. Stated that patients with schizophrenia should be prescribed AAs.
NSF (National Service Framework) for Mental Health, (DH, 1999b)	Sets national standards and defines national service models in mental health; local action and national underpinning programmes for implementation; and a series of milestones to assure progress, with performance indicators to support effective performance management.
Effective Health Care Bulletins - Cochrane Schizophrenia Group, 1999	Systematic review of 11,390 participants in 19 studies involving AAs (amisulpride; clozapine; quetiapine olanzapine; risperidone; zotepine; ziprasidone) vs CAs. The bulletin was produced in December 1999 by the NHS Centre for Review and Dissemination at the University of York, based on work they had conducted for the NICE Technology Appraisal on AAs, which was not published until 2003. The conclusion was that AAs "may be a further refinement, but not a revolution, in the care of those with schizophrenia". Potentially reduced the impact of the later published NICE guidance.
Geddes *et al*., 2000 Meta-analysis	Meta-analysis: 12, 649 participants in 52 randomised trials involving AAs (amisulpride; clozapine aripiprazole; quetiapine olanzapine; risperidone; sertindole) vs CAs (haloperidol or chlorpromazine). No clear evidence that AAs are more effective or are better tolerated than CAs. Dose of CAs used explained heterogeneity in results. When haloperidol dose (or equivalent) was ≤12mg/day, AAs had no benefits in terms of efficacy or tolerability, but caused fewer EPS. When comparator doses were too high, this disadvantaged CAs, as it caused the early emergence of EPS followed by early dropout rates.
NICE TA (Technology Appraisal) guidance, 2002a (Atypical Antipsychotics)	Systematic review of 172 randomised controlled trials involving AAs (amisulpride; olanzapine; quetiapine, risperidone; zotepine) vs CAs, of which 29 were head to head; 53 studies were either case-control, had more than 2 years follow up or more than 2,000 participants. The mandatory NHS guidance stated: “for new patients AAs should be considered within the choice of first-line treatments for patients with newly diagnosed schizophrenia. In patients on CAs with adequate symptom control, but with unacceptable side effects, or for those in relapse who have previously experienced unsatisfactory management with CAs, then AAs should be considered. Patients on CAs with good control of their condition, without unacceptable side effect control should not be switched to AAs”.
NICE Clinical Guideline, 2002b (Schizophrenia)	Practice and service guidelines for schizophrenia. Refers to NICE technology appraisal for guidance in relation to AAs.
Davis *et al*., 2003 Meta-analysis	Meta-analysis of 18,272 patients in 124 randomised trials involving AAs (amisulpride; clozapine; olanzapine; quetiapine; risperidone; ziprasidone) vs CAs (haloperidol or chlorpromazine). Some AAs more efficacious than CAs. Effect size of clozapine, amisulpride, risperidone and olanzapine significantly greater than CAs. No difference detected between amisulpride, risperidone and olanzapine.

Table 4.9: Atypical Antipsychotics - Timeline Commentary for Safety and Regulatory Events

Note: Not all licensing events that appear on the timeline are represented in the table below. Ony those events that required additional context are presented.

Events	Description
Restricted reintroduction of clozapine 1990	Clozapine was the first atypical, but was voluntarily withdrawn in 1975 as it was associated with a high risk of agranularcytosis (a potentially fatal reduction in white blood cells) and seizure. It was reintroduced with strict monitoring requirements in 1990 following psychiatrists' requests to reinstate the drug based on its efficacy in refractory patients (demonstrated in the trial by Kane *et al*., 1988).
Risperidone launch – schizophrenia Jun 1993	With clozapine being reserved for second-line use, risperidone had to compete with a generic market, but its increased cost was not believed tobe an issue when there was such a need for a new pharmacological intervention.
Remoxipride - withdrawn UK Feb 1994	Remoxipride withdrawn in 1994 due to reported side effects of aplastic anaemia.
Olanzapine launch – schizophrenia Oct 1996	With olanzapine, there was no need for titration, which ultimately translated to ease of use for psychiatrists and patients. Olanzapine entered at an even higher acquisition cost compared with risperidone.
Zeneca / Astra AB merger Apr 1999	Quetiapine was initially developed by Zeneca and launched prior to the merger with Astra AB in 1999, which later increased the resources available to promote the drug.
Sertindole-withdrawn UK 1999	Sertindole was the third AA to be withdrawn due to safety concerns. It was voluntarily withdrawn in 1999 due to cases of arrhythmias and sudden cardiac death, but was later reintroduced under special prescribing conditions.
Olanzapine Velotab launch Jan 2000	The first orodispersible formulation called Velotab developed for patients unable or unwilling to take tablet forms. Once in contact with saliva, it dissolves instantly so the patient is unable to spit it out.
Metabolic issues (diabetes) Apr 2002	Dawning of adverse metabolic effects with regard to AAs and diabetes. Data mining analysis over 4 months of 38,632 patients with a diagnosis of schizophrenia and diabetes. Clozapine, olanzapine, quetiapine; risperidone vs CAs. Prevalence of diabetes was significantly increased for patients who received clozapine, olanzapine and quetiapine, but not risperidone (Sernyak *et al*., 2002). Committee on Safety of Medicines released a pharmacovigilance statement with reference to olanzapine recommending clinical monitoring for hyperglycaemia in diabetic patients. In 2003, the FDA required all AAs to carry warnings of hyperglycaemia and diabetes.
Olanzapine launch - bipolar Jun 2002	All three drugs now have additional indications for mania in bipolar disorder, but Lilly designed their clinical trial programmes to enable olanzapine to be the first AA to obtain the additional licence ahead of risperidone. Bipolar disorder causes alternating periods of depression and mania (abnormally elevated or irritable mood) or 'mixed episodes' where people have symptoms of both depression and mania.
Risperdal (risperidone) Consta – long-acting IM launch Aug 2002	The first long-acting intramuscular depot injection called Risperdal Consta administered once every 2 weeks. It conferred a lower risk of relapse due to non-compliance and widened the choice of treatments for patients with psychotic illnesses.
Risperidone Quicklet launch Jan 2003	Quicklets were tablet forms of rispiridone designed to dissolve on the tongue and swallowed without the need for water.
Metabolic issues (cholesterol) Feb 2003	Dawning of adverse metabolic effect with regard to AAs and raised cholesterol. Randomised double-blind 14 week trial in 157 patients. Clozapine, olanzapine, risperidone vs haloperidol. Clozapine, olanzapine and haloperidol were associated with a significant increase in plasma glucose levels. Clozapine and olanzapine were associated with a significant increase in cholesterol levels. (Lindenmayer *et al*., 2003).
Quetiapine launch – bipolar Jan 2004	Quetiapine became the first AA to treat both the depressive and manic episodes associated with bipolar.
Olanzapine - Rapid-acting IM launch Feb 2004	Lilly launched the first rapid-acting intramuscular formulation called Zyprexa IM for rapid control of agitation.
Safety warning – elderly Mar 2004	'Dear Dr' letter released in March 2004 (MHRA, 2004a) in response to the Committee on the Safety of Medicines guidance to doctors stating that risperidone and olanzapine should no longer be prescribed for the treatment of behavioural symptoms in elderly patients with dementia due to the risk of cerebrovascular adverse events (stroke) and death. Neither drug was licensed for this indication, but were used off-label

4.4. Case Study 3: PDE5 Inhibitors for Erectile Dysfunction

Phosphodiesterase type 5 (PDE5) inhibitors are oral drugs taken as needed by men with erectile dysfunction (ED) prior to planned sexual activity. They are potent, reversible, competitive inhibitors of the PDE5 enzyme. By blocking this enzyme, which degrades cyclic guanosine monophosphate (the chemical messenger responsible for triggering increased blood flow to the penis), erections can be sustained. PDE5 inhibitors therefore amplify the response to sexual arousal rather than cause an erection *per se*.

Erectile Dysfunction

Erectile dysfunction is defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance (National Institutes of Health, 1993). Despite being primarily attributed to psychogenic causes, in men aged over 50 years, ED is now considered to be mainly organic in origin resulting from vascular, hormonal or neurological complications (Kaiser, 1999).

The PDE5 inhibitor class consists of three drugs listed in Table 4.10. Interviews were conducted with Pfizer, Lilly and Bayer, regarding sildenafil, tadalafil and vardenafil respectively.

Table 4.10: The PDE5 erectile dysfunction market

Drug	Brand name	Manufacturer	Market hierarchy	Market entry position	UK launch
Sildenafil citrate	Viagra	Pfizer	1	1st	Sep 1998
Tadalafil	Cialis	Lilly	2	2nd	Feb 2003
Vardenafil hydrochloride	Levitra	Bayer	3	3rd	Mar 2003

All three have similar efficacy and toxicity profiles, but differences in the time of onset of action, the period of responsiveness and the conditions under which the drug is administered i.e. whether absorption is affected by food and alcohol impact on patient preference (Table 4.11).

Table 4.11: Pharmacokinetic characteristics of PDE5 inhibitors (based on data from Wright, 2006)

PDE5 inhibitor	Licensed dose (range)	Onset of action	Peak plasma levels	Median plasma half-life	Period of action	Administration conditions
Sildenafil	50mg (25-100mg)	60 mins (35% ≤14 mins)	1h	4h	6-8h	Absorption delayed by food.
Tadalafil	10mg (10-20mg)	30 mins (16% ≤16 mins)	2h	17.5h	24h (up to 36h)	Unaffected by food.
Vardenafil	10mg (5-20mg)	25-60 mins (21%≤ 10 mins)	1h	4h	4-5h	Absorption delayed by food.

Figure 4.5 shows the diffusion curves for the PDE5 inhibitor class. Figure 4.6 shows the literature and expert augmented timelines for sildenafil, tadalafil and vardenafil. Commentaries of the events represented in each timeline are presented in Tables 4.12 to 4.14.

Figure 4.5: PDE5 Inhibitors - Diffusion Curves

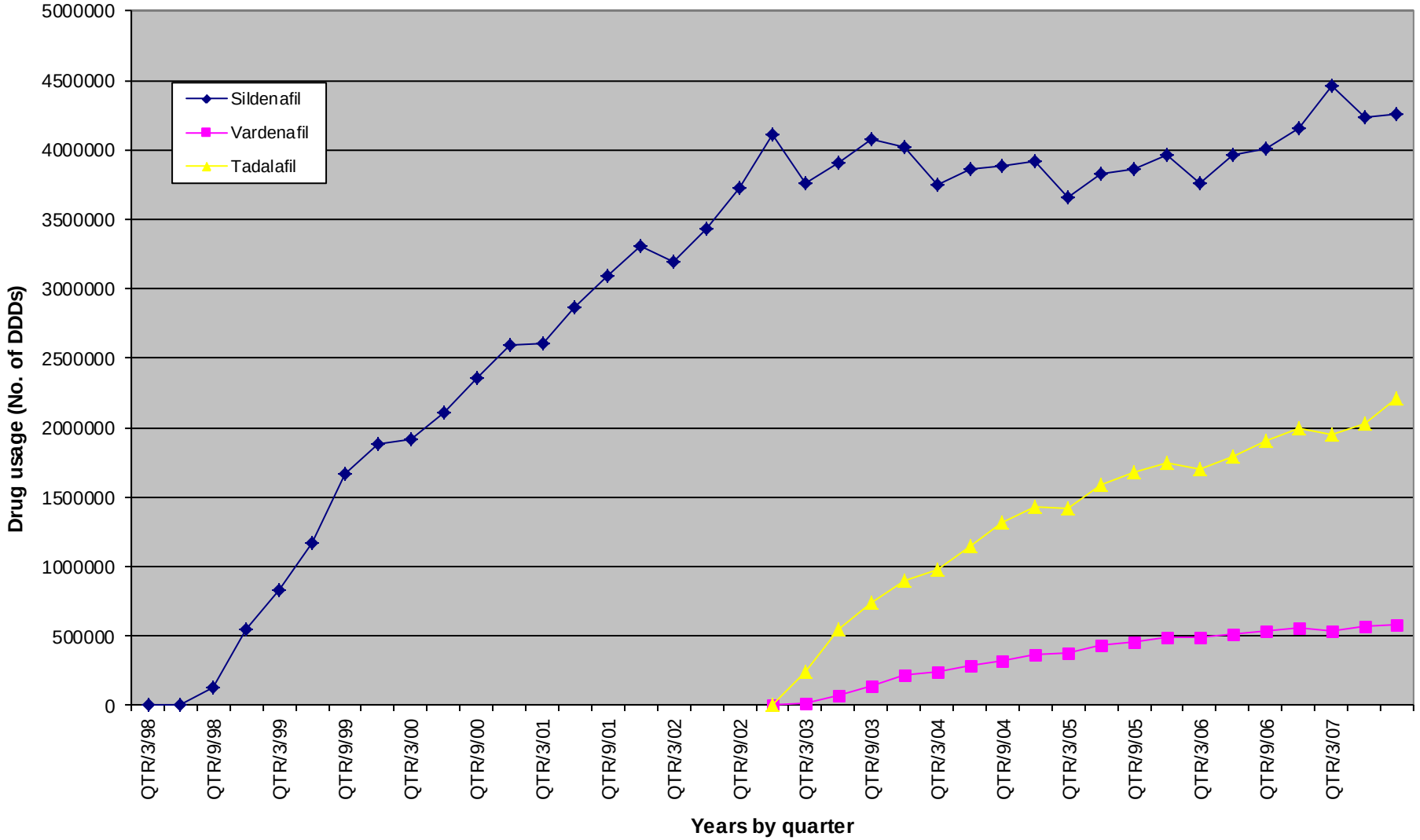
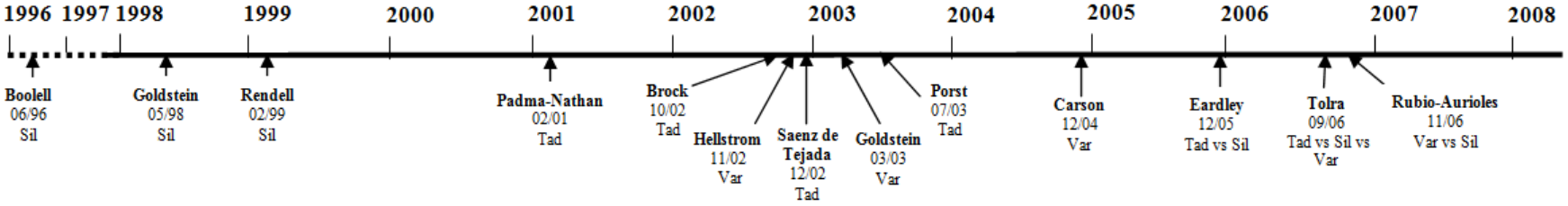
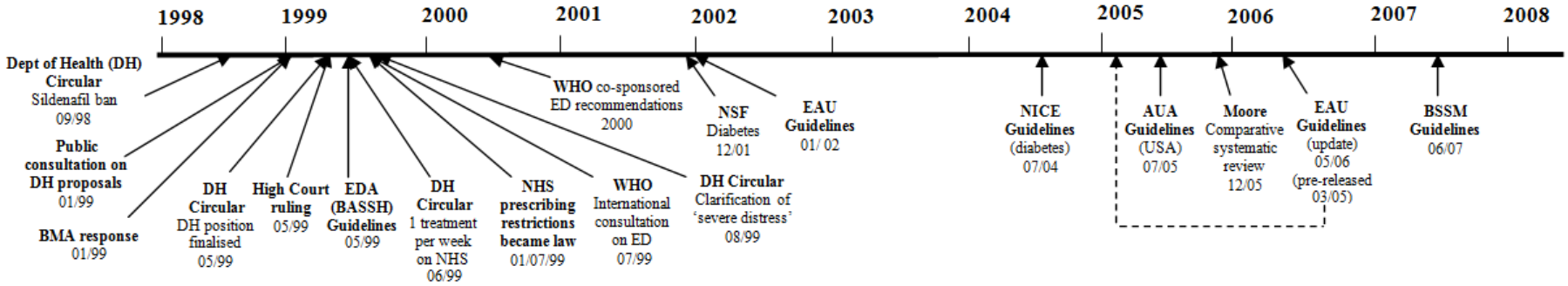


Figure 4.6: PDE5 Inhibitors - Timeline of Literature and Expert-derived Diffusion Factors

Primary – Research Trials (See Table 4.12 for commentary) **Key: Sil = sildenafil; Tad = tadalafil; Var = vardenafil**



Secondary – Guidelines/Reviews/Policy (See Table 4.13 for commentary)



Regulatory/ Licensing (UK) (See Table 4.14 for commentary)

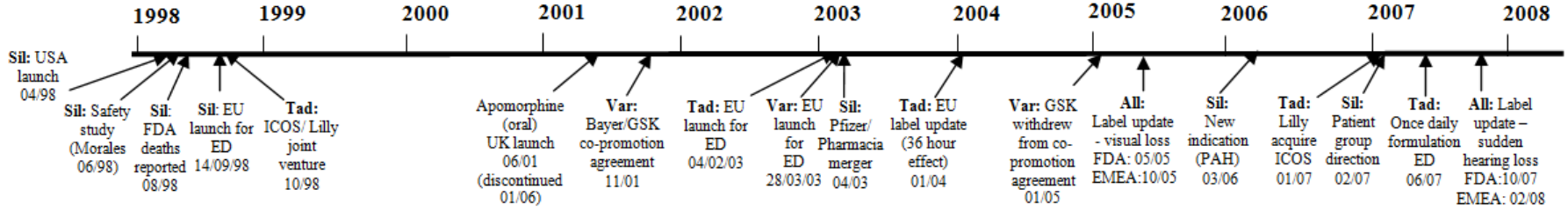


Table 4.12: PDE5 Inhibitors - Timeline Commentary for Primary Level Evidence

Evidence summary:

- Efficacy studies had only been conducted against placebo at the point when the interviews were conducted. Differences between selection criteria in studies of the three drugs (particularly in the way patients previously treated with sildenafil were included or excluded), and differential reporting of outcomes between trials also prevented direct comparison of efficacy (efficacy in ED studies is usually assessed by patient-rated outcome measures from self-administered questionnaires) (Hackett *et al*., 2008). For consistently reported efficacy outcomes, all three drugs are similar, with rates of successful intercourse and improved erections between 59-65% and 71-76%, respectively versus placebo rates of 22-28% for both outcome measures (Moore *et al*., 2005).

- Trial programmes followed a similar course for all three drugs i.e. demonstration of efficacy initially in a wide ED etiology, followed by subsequent studies in challenging to treat subpopulations. Quoted efficacy rates are lower for patients with diabetes (50-55%), and after nerve-sparing radical prostatectomy (37-41%) (Hackett *et al*., 2008). The recognisable differing pharmacological characteristics made it difficult to conduct randomised, double-blind, comparative studies, so head to head comparisons have been based on preference studies, many of which have been criticised for poor design that has introduced bias (Mulhall and Montorsi, 2006). One study that compared all three PDE5 inhibitors, demonstrated a preference for tadalafil based on its longer period of action (Tolra *et al*., 2006).

Pivotal clinical trials were mostly determined through assessment of the literature as a result of limited clinical expert input for this section.
Key:
* Highlighted as major trials in 'Key Clinical Trials in Erectile Dysfunction' by Carson (2007) - identified equivalent trials for tadalafil and vardenafil.
** Highlighted as trials of major importance in Hellstrom, 2003.
*** Highlighted as major trials in the British Society for Sexual Medicine (BSSM) guidelines (preference studies).

Trial	Study drugs	Importance	Study design	Outcome
Boolell *et al*., 1996*	Sildenafil vs placebo. ED of no obvious organic cause.	First significant publication on an oral therapy for ED.	Small randomised double-blind, 4-way crossover trial (phase II) in 12 men. Sildenafil (10, 25 or 50mg) or placebo received in a crossover design on 4 different study days (min 3 days between treatments): design enabled evaluation with a relatively small sample size.	Significantly longer mean duration of >60% rigidity with sildenafil during visual sexual stimulation at the base of penis: 3.2 mins (placebo) vs 31.8 mins (50mg) and at tip of the penis: 3.0 mins (placebo) vs 26.5 mins (50mg). Mild headache reported by 4 patients at 10 and 25mg doses.

Trial	Study drugs	Importance	Study design	Outcome
Goldstein *et al*., 1998*	Sildenafil vs placebo. ED of various aetiologies.	Pivotal phase III trial unequivocally demonstrated benefit of sildenafil in mild to severe ED.	Two sequential, multicentre studies in 861 patients. 1. Dose-response study: Double-blind study in 532 men randomised to receive placebo or 25, 50 or 100mg sildenafil for 24 weeks (no more than 1 dose per day). 2. Dose-escalation study with open-label extension: 329 men randomised to placebo or sildenafil (50mg). Patients able to halve or double dose depending on response over 12 weeks.	In the dose-response study, improved erections were reported by 56%; 77% and 84% of the men taking 25mg, 50mg and 100mg sildenafil respectively vs 25% placebo. In the dose escalation study, 69% of all attempts at sexual intercourse for men receiving sildenafil (50mg) were successful vs 22% with placebo. Headache, flushing and dyspepsia were the most common adverse effects.
Rendell *et al*., 1999**	Sildenafil vs placebo in men with ED and diabetes (type 1 or type 2).	First major study in a challenging to treat subpopulation.	Multicentre, double-blind, trial in 268 men with diabetes randomised, to receive sildenafil 50mg (n=136) with the option to increase or reduce dose according to response (no more than one dose per day) or placebo (n=132) for 12 weeks.	At least 1 successful attempt at sexual intercourse was reported by 61% of men receiving sildenafil vs 22% placebo. Improved erections reported by 56% of men receiving sildenafil vs 10% placebo. Adverse events: headache (11% sildenafil, 2% placebo), dyspepsia (9% vs 0%) and respiratory tract disorder (6% vs 2%). Incidence of cardiovascular events comparable for both groups.
Padma-Nathan *et al*., 2001*	Tadalafil vs placebo. ED various aetiologies.	First major trial demonstrating efficacy and safety of a new PDE5 inhibitor to rival sildenafil – no reference to longer period of action.	Multicentre double-blind, phase II study in 179 men randomised to receive tadalafil (2-25mg) or placebo for 3 weeks. Equivalent study in vardenafil published 6 months later in Aug 2001 (Porst *et al*., 2001).	69.8% and 70.2% of attempts at sexual intercourse for men receiving 10mg and 25mg tadalafil, respectively were successful vs 26.6% with placebo. Improved erections reported by 80.6% in groups receiving both 10mg and 25mg tadalafil vs 17.1% placebo. Common adverse events included headache and dyspepsia. No alterations of colour vision reported (side effect associated with sildenafil).
Brock *et al*., 2002 *	Tadalafil vs placebo. ED of various aetiologies).	Study unequivocally demonstrated benefit of tadalafil in mild to severe ED.	Integrated analysis of 5 x 12 week, randomised, double-blind, placebo-controlled, parallel group trials conducted at 74 centres in 1,112 men. Tadalafil doses used in included studies ranged from 2.5mg - 20mg (individual trials not specified).	61% and 75% of intercourse attempts were successful at doses of 10mg and 20mg, respectively, compared with 32% with placebo. Improved erections reported by 81% receiving 20mg tadalafil, vs 35% placebo. Results were similar irrespective of the time the dose was taken between 4 and 36 hours previously.
Hellstrom *et al*., 2002**	Vardenafil vs placebo. ED of various aetiologies.	First pivotal phase III results showing key efficacy and safety profile of vardenafil.	Multicentre double-blind, phase III study in 805 men randomised to receive vardenafil (5-20mg) or placebo for 26 weeks.	64.7% and 66.7% of attempts at sexual intercourse for men receiving vardenafil 10mg and 20mg, respectively were successful vs 32.7% with placebo. Improved erections reported by 79.8% and 85.2% receiving 10mg and 20mg vardenafil, respectively vs 27.6% placebo at week 26. Common adverse events included headache, rhinitis, flushing and dyspepsia. No blue colour vision disturbances reported (side effect associated with sildenafil).
Saenz de Tejada *et al*., 2002 **	Tadalafil vs placebo in men with ED and diabetes (mainly type 2).	First major study of tadalafil in challenging to treat patients.	Multicentre double-blind, phase III study in 216 men with type 1 or type 2 diabetes randomised to receive tadalafil (10 or 20mg) or placebo up to once daily for 12 weeks.	28.4% of men taking tadalafil 10mg, and 29.1% taking 20mg achieved successful intercourse compared with 1.9% placebo. Improved erections reported in 56%, and 64% taking tadalafil doses 10mg and 20mg, respectively vs 25% placebo. Adverse events were representative of the PDE5 inhibitor profile.

Trial	Study drugs	Importance	Study design	Outcome
Goldstein *et al*., 2003 **	Vardenafil vs placebo in men with ED and diabetes (type 1 or type 2).	First study of vardenafil demonstrating significant improvement in erectile function in 'challenging to treat' categories.	Multicentre double-blind, phase III study in 452 men with diabetes randomised to receive vardenafil (10mg or 20mg) or placebo as needed for 12 weeks.	49% and 54% of attempts at sexual intercourse for men receiving vardenafil 10mg and 20mg, respectively were successful vs 23% with placebo. Improved erections reported by 57% and 72% receiving 10mg and 20mg vardenafil, respectively vs 13% placebo at week 12. Common adverse events included headache, rhinitis and flushing.
Porst *et al*., 2003	Tadalafil vs placebo in men with ED of various aetiologies.	Major study demonstrating the extended period of action of tadalafil up to 36 hours.	Multicentre double-blind, randomised, phase III study in 348 men randomised to receive tadalafil (20mg) or placebo for a total of 8 weeks. The 8 weeks was divided into two 4-week intervals where patients were requested to attempt sexual intercourse approximately 24 or 36 hours after tadalafil or placebo dosing.	Effectiveness evident up to 36 hours after ingestion. At 24 hours 52.9% of intercourse attempts successful vs 29.1% with placebo. At 36 hours, 59.2% of intercourse attempts successful vs 28.3% with placebo. Adverse events included headache, flushing, dyspepsia and myalgia.
Carson *et al*., 2004 (PROVEN study)	Vardenafil vs placebo in men with ED unresponsive to sildenafil.	First major trial in sildenafil non-responders – presented ahead of publication at Sexual Medicine Society of North America in Oct 2003.	Multicentre, double-blind, randomised, 12-week, flexible-dose trial involving 463 men with ED (diabetic and non-diabetic) unresponsive to sildenafil (by history). Patients received placebo or vardenafil 10mg with the option to maintain dose or titrate by one dose level (5, 10 or 20mg) based on efficacy and tolerability at 4 and 8 weeks.	46.1% of men taking vardenafil achieved successful intercourse compared with 16.1% placebo. Improved erections reported by 61.6% receiving vardenafil vs 15% placebo at week 12. Adverse events were representative of the PDE5 inhibitor profile.
Comparative preference studies				
Eardley *et al*., 2005***	Tadalafil vs sildenafil. ED of various aetiologies.	First head to head study based on preference.	Multicentre, open-label, cross-over study in 367 PDE5 inhibitor-naïve men randomised to receive sildenafil (25-100mg) for 12 weeks followed by tadalafil (10-20mg) for 12 weeks or vice versa (8 weeks of dose optimisation followed by 4 weeks of assessment). Patients then chose which treatment to continue during an 8 week extension.	Patient preference for tadalafil (71%) versus sildenafil (29%). Major reason for preference was the ability to get an erection long after taking the drug. Efficacy of both drugs was very similar.
Tolra *et al*., 2006***	Sildenafil vs vardenafil vs tadalafil. ED of various aetiologies.	First comparative preference study incorporating all PDE5 inhibitors.	Open-label, fixed dose, cross-over study in 132 PDE5 inhibitor-naïve men randomised to sildenafil (100mg), tadalafil (20mg) or vardenafil (20mg). Drugs were taken at least 6 times over a period of 45-60 days with a washout period of 7 days.	52% favoured tadalafil, 28% sildenafil and 20% vardenafil, with the possibility of achieving an erection well after taking the drug being the main reason for preference. Efficacy rates were similar for all three drugs.
Rubio-Aurioles *et al*., 2006 ***	Vardenafil vs sildenafil in men with ED and diabetes, hypertension and/or hyperlipidaemia.	First double-blind preference study.	Double-blind, fixed-dose, pooled (prospective analysis on 2 studies) cross-over study in 1,057 men randomised to receive sildenafil (100mg) or vardenafil (20mg) for 4 weeks. Following a 1 week washout, patients switched treatment for 4 weeks. Previous users of sildenafil included provided they had not used medication for 4 weeks prior to study start.	Study demonstrated a 38.9% versus 34.5% preference in favour of vardenafil with 26.6% expressing no preference. Efficacy was similar for both drugs.

Table 4.13: PDE5 Inhibitors - Timeline Commentary for Secondary Level Evidence and Policy

Secondary Evidence and Policy	Description
Dept of Health (DH) Circular: Sildenafil ban (HSC 1998/158) **(DH, 1998)**	The Secretary of State for Health issued a Health Service Circular (HSC 1998/158) placing a *de facto* ban on prescribing sildenafil on the NHS on the eve of its EU launch pending further consultation. It stated "doctors should not prescribe sildenafil until further notice. Health authorities are also advised not to support the provision of sildenafil by NHS Trusts other than in exceptional circumstances, which are required to be cleared in advance".
Public consultation on DH proposals,	The DH released a 6 week consultation document proposing restricting access to sildenafil on the NHS under Schedule 11 of the 1992 General Medical Services regulations to 6 patient groups (patients with diabetes; multiple sclerosis; prostatectomy; radical pelvic surgery; spinal cord injury; single gene neurological disease). A patient also qualified if a) they were receiving a course of NHS drug treatment for ED due to any condition on 14th September 1998; or b) were suffering "severe distress" on account of their ED - determined only after specialist assessment. These restrictions were an attempt to limit the cost of ED treatment to around £10-12 million/year.
BMA (British Medical Association) response	The BMA condemned the proposals believing it was setting a dangerous precedent to discriminate against patients with equal clinical need. Following legal advice indicating the guidance to be unlawful, the BMA advised its members to disregard the restrictions and prescribe sildenafil to all patients who had a demonstrable clinical need, until such time that the Government guidelines were given the force of law (Abbasi, 1999). Some GPs had already taken the decision to ignore the ban, believing it to be in contravention of GPs' terms of service, which placed an obligation on them to respond to patient need.
DH circular: DH position finalised (HSC 1999/115) **((DH, 1999c)**	In response to the consultation, the final DH position included a further 6 patient groups who could receive treatment for ED on the NHS under Schedule 11(patients with renal failure treated by dialysis or transplant; spina bifida; poliomyelitis; Parkinson's disease; severe pelvic injury; or men receiving treatment for prostate cancer). The impact of these restrictions was that only around 17% of men were eligible to receive sildenafil on the NHS.
High Court ruling	Pfizer challenged the initial September 1998 ban in the High Court, claiming the decision was unprecedented and discriminatory and was in breach of EU law by asking doctors to act contrary to their ethical duty and terms of service. While accepting that the circular was not a ban as such, its effect was to act as a ban and that was the intention. The DH argued it was interim advice while consultations took place before a final policy was decided upon. The High Court ruled in Pfizer's favour stating the Government had acted unlawfully under English law by deterring doctors from exercising their duty to use clinical judgement, and under EU law as it contravened the European Transparency Directive, which requires that reasons for exclusion must be based on objective and verifiable criteria (Dyer, 1999). Drugs can only legally be rationed with Parliamentary approval, which the Government only later sought to do.
EDA (Erectile Dysfunction Alliance) Guidelines, 1999 - later became British Association for Sexual Health and HIV (BASHH)	Recommended that treatment should be determined according to patient choice. Sildenafil was recommended (with the caveat of use being dependent on local/national availability) amongst other currently used therapies including intracavernosal injection of alprostadil, intraurethral alprostadil, or vacuum devices. The same guidelines were later published in the BMJ (Aug 2000) by guideline contributors Ralph and McNicholas.
DH circular: 1 treatment per week (HSC 1999/148) (**DH, 1999d)**	Policy restricted access to one treatment per week on the NHS based on i) data suggesting men aged 40-60 have sex once a week and ii) concern over the street value of some treatments for impotence leading to unlicensed use of these treatments. Doctors were allowed to use their discretion if more frequent dosing was deemed necessary.
DH circular: Clarification of 'severe distress' (HSC 1999/177) (**DH, 1999e)**	In response to the term 'severe distress' being considered obscure (thereby placing a heavy burden on specialist services from referrals), the DH provided clarification on the identification and management within specialist services of those men diagnosed as suffering severe distress on account of their ED to avoid misinterpretation of this exemption category.
WHO co-sponsored recommendations Jardin *et al*., 2000	Recommended oral therapies as first-line treatment for ED (based on first international consultation on ED).
NSF (National Service Framework) for Diabetes, 2001 (DH, 2001b)	Indicated the need for regular surveillance for, and effective management of, other conditions that occur more commonly in people with diabetes, such as depression and ED, which can impact on the quality of life of people with diabetes.
EAU Guidelines (European Association of Urology) Wespes *et al*., Jan 2002 (update:Wespes *et al*., May 06)	The 2002 guidelines recommended oral therapies (including sildenafil and apomorphine), vacuum devices or psychosexual therapy as first-line therapies. In the 2006 update (published in advance in report form in Mar 05), while the three available PDE5 inhibitors were included as first-line therapies, the absence of controlled studies comparing efficacy or tolerability resulted in recommendations that patients be informed of the effects and possible disadvantages of each drug, as well as how to use the drug, and that each drug should be administered at least 4 times before being considered to be non-effective and replaced by another PDE5 inhibitor.

Secondary Evidence and Policy	Description
NICE Clinical Guideline (diabetes type 1), 2004a	Recommended that men with type 1 diabetes should be asked annually whether ED was an issue and offer a trial of a PDE5 inhibitor drug if appropriate (no distinction was made as to the choice of PDE5 inhibitor). While ED was also featured prominently in Clinical Guideline 66: The management of type 2 diabetes, it was not published until May 2008, which was outside the time frame of the timeline and none of the former clinical guidelines on type 2 diabetes that it replaced (G, H, F, E) made any reference to ED.
AUA Guidelines (American Urological Association) Montague *et al*., 2005	Oral PDE5 inhibitors, unless contraindicated should be offered as a first-line of therapy for erectile dysfunction. At the time of publication there was insufficient evidence to support the superiority of one agent over the others. Prior to proceeding to other therapies, patients reporting failure of PDE5 inhibitor therapy should be evaluated to determine whether the trial of PDE5 inhibition was adequate.
Moore *et al*., 2005 Meta-analysis	There are several meta-analyses of individual drugs, but none determined to be of major significance. Moore *et al.*, 2005 was the first meta-analysis to compare all 3 PDE5 inhibitors, involving 12,580 participants in 50 randomised, double-blind, placebo-controlled trial (35 sildenafil trials in 7,135 men; 8 tadalafil trials in 2,071 men and 7 vardenafil trials in 3,374 men). Differences in trial outcomes reported limited comparisons, and the most useful outcomes were not reported. For common outcomes there was a similar efficacy between PDE5 inhibitors. All three drugs were well tolerated, with headache being the most commonly reported, and few serious adverse events.
BSSM Guidelines (British Society for Sexual Medicine) Hackett *et al*., 2008 (available online from June 07)	Recommended PDE5 inhibitors as first-line therapy and that at least 8 doses should be given before a man is considered a non-responder (emphasised the importance of adequate testosterone levels to achieve maximal response with PDE5 inhibitors). In non-responders second–line (intracavernous injection therapy or intraurethral alprostadil), or third-line therapies (penile prostheses) should be offered. Also highlighted the link between ED and cardiovascular disease, indicating need for presenting ED patients to be evaluated for cardiovascular and endocrine risk factors, and vice versa.

Table 4.14: PDE5 Inhibitors - Timeline Commentary for Safety and Regulatory Events

Note: Not all licensing events that appear on the timeline are represented in the table below. Ony those events that required additiona context are presented.

Events	Description
Sildenafil USA launch Apr 1998	The mass media attention that followed the USA launch of sildenafil raised levels of interest and expectations of the general public and clinicians in the UK ahead of its launch 5 months later.
Sildenafil safety study (Morales *et al.*, Jun 1998)	In response to mounting cardiovascular safety concerns, high priority was given to rapidly peer-review a large scale study assessing safety data from 18 randomised controlled trials and 10 open-label studies in over 3,700 men, which detected no statistically significant difference in the incidence of myocardial infarction (MI) in sildenafil and placebo recipients.
Sildenafil FDA deaths Aug 1998	Just ahead of sildenafil's European launch, the FDA reported 123 deaths linked with use of the drug. Most patients had one or more risk factors for cardiovascular disease contraindicating the use of sildenafil. Theories at the time pointed not to a direct side effect but to a strain on the heart from the physical exertion of sexual activity.
Tadalafil: ICOS/Lilly joint venture Oct 1998	Tadalafil was originally developed by ICOS Corporation in 1993, but shortly after phase II trials began, Lilly entered into a joint venture with ICOS to commercialise the drug.
Apomorphine launch Jun 2001	Sublingual apomorphine (Uprima) was the first competitor to challenge sildenafil as another oral drug for ED. It had a faster onset of action of around 15 minutes compared with sildenafil which was around one hour.
Bayer/GSK co-promotion agreement Nov 2001	Bayer entered a co-promotion agreement with GlaxoSmithKline (GSK) for vardenafil in November 2001. Bayer was responsible for all regulatory and manufacturing activities, while both companies shared expenses for marketing.
Sildenafil: Pfizer/Pharmacia merger Apr 2003	In 2003, Pfizer acquired Pharmacia, becoming the largest pharmaceutical company in the UK.
Tadalafil: Label update (36 hour effect) Jan 2004	Tadalafil was initially launched on the basis of a longer period of action, but it was not until a year after launch that the label was updated to indicate a 36-hour duration of effect from a single dose (for which it gained notoriety as the 'weekend pill'). This disconnected the act of taking the tablet from intimacy, thereby removing the associated time pressures and restoring an element of spontaneity.
Vardenafil: GSK withdrew from co-promotion agreement Jan 2005	In January 2005, GSK withdrew from the co-promotion agreement, transferring all rights back to Bayer in Europe, whilst retaining the arrangement in the USA. The decision was believed to reflect disappointing sales of the product.
All: Label update -visual loss 2005	While the FDA were unable to conclude a cause and effect relationship between the use of PDE5 inhibitors and non-arteritic anterior ischaemic optic neuropathy (NAION), they required that all PDE5 inhibitor product labels be updated to advise patients to stop treatment in the sudden event of loss of vision in one or both eyes. PDE5 inhibitors are also contraindicated in patients with pre-existing retinitis pigmentosa. The EMEA followed with an update to the Summary of Product Characteristics (SPC) for all PDE5 inhibitors five months later.
Sildenafil: New indication (PAH) Mar 2006	Sildenafil was the first PDE5 inhibitor to receive an additional licence for the treatment of adult patients with pulmonary arterial hypertension classified as WHO functional class II and III, under the brand name Revatio to improve exercise capacity.
Lilly acquire ICOS Jan 2007	Lilly later purchased ICOS Corporation in 2006, gaining complete ownership of tadalafil.
Sildenafil: Patient Group Direction Feb 2007	Sildenafil was launched without the need for an individual doctors' prescription in three high street pharmacies in Manchester on Valentine's Day. While it remained a prescription only medicine, it could be distributed under a Patient Group Direction allowing pharmacists to provide an initial pack of four tablets following a consultation. The patient was then required to see a private doctor by the pharmacy to buy further pills (Mayor, 2007).
Tadalafil: once daily formulation Jun 2007	Tadalafil once daily was launched in the UK in July 2007 for patients who have previously responded to an on-demand PDE5 inhibitor, but who required use at least twice weekly. At a recommended dose of 5mg daily, men can attempt sexual activity at any time between doses.
All: Label update - sudden hearing loss 2008	The FDA announced label revisions to all PDE5 inhibitors to include a more prominent warning of the potential risk of sudden hearing loss. While no causal relationship could be established (as with NAION), the FDA believed there was a strong temporal relationship. In almost all cases hearing loss was unilateral, and temporary in around a third of cases. The EMEA followed with an update to the SPC of all PDE5 inhibitors four months later.

4.5. Case Study 4: Statins for the prevention of first and recurrent cardiovascular events through lipid lowering

Statins, or hydroxmethylglutaryl-CoA (HMG-CoA) reductase inhibitors, are oral therapies used to lower cholesterol in people with prior evidence of cardiovascular disease (CVD) (secondary prevention), or those at increased risk but with no overt evidence of CVD (primary prevention). Statins impede atherosclerosis, reduce heart attacks, strokes and cardiac death.

Cardiovascular Disease

CVD is defined as disease of the heart and blood vessels. CVD causes one in three deaths and for every one fatality, there are at least two people who have a major non-fatal CVD event. It commonly manifests as coronary heart disease (CHD), also known as coronary artery disease and ischaemic heart disease, and is caused by an accumulation of a fatty material called atheroma that narrows the arteries that supply the heart. The narrowing can cause myocardial infarction (MI) and angina. Other forms of CVD include peripheral arterial disease, stroke and transient ischaemic attack.

The World Health Organization estimates that blood cholesterol levels in excess of 3.8 millimoles per litre (mmol/L) are responsible for more than 50% of CVD events (WHO, 2002). Cholesterol, particularly low-density lipoprotein cholesterol (LDL-C), which makes up around two thirds of total serum cholesterol (TC) plays a major role in initiating the development of atherosclerotic plaque. Extensive lipid accumulation and inflammation can then cause the plaque to rupture (NICE, 2006). In England, the average TC concentration in adults is approximately 5.6mmol/L, of which LDL-C

comprises an average of 3.6mmol/L (NICE, 2007b). National guidelines and policies have set TC and LDL-C goals of less than 5mmol/L and less than 3mmol/L respectively, as a definition of adequate care (Department of Health, 2000).

Table 4.15: Risk classification based on lipid profile (adapted from the National Cholesterol Education Programme Adult Treatment Panel classification, 2001)

Classification	**TC** (mmol/L)	**LDL-C** (mmol/L)
Optimal	<5.2	2.6 - 3.3
Borderline high	5.2 - 6.2	3.4 - 4.1
High	>6.2	4.2 - 4.9
Very high	-	>5.0

Statins are recommended for all high risk patients with established atherosclerotic disease (secondary prevention), in most people with diabetes who are at risk of CVD, and others with a 20% or greater 10 year risk of developing CVD (primary prevention) (NICE, 2006). This accounts for an estimated one quarter of adults aged 30-75 (around 7 million people in the UK) (Laurie, 2008). Currently, one in five prescriptions for patients with heart and circulatory diseases are for statins (Trusler, 2011).

There are five statins available in the UK: simvastatin (Zocor, MSD), atorvastatin calcium (Lipitor, Pfizer), fluvastatin (Lescol, Novartis), rosuvastatin calcium (Crestor, AstraZeneca), pravastatin (Lipostat, BMS). Cerevastatin (Lipobay, Bayer) was withdrawn from the UK market in 2001 due to safety concerns. Simvastatin was the first statin to become available generically in May 2003, followed by pravastatin in August 2004. Market entry and hierarchy positions are outlined in Table 4.16. Interviews were conducted with Pfizer and AstraZeneca regarding atorvastatin and rosuvastatin[12], respectively. Although simvastatin was discussed as an example during

[12] Two separate interviews were conducted with AstraZeneca on rosuvastatin

the general interviews with MSD, it was not possible to secure a separate interview to discuss this drug specifically.

Table 4.16: The statin lipid lowering market

Drug	Brand name	Manufacturer	Market hierarchy	Market entry position[13]	UK launch
Simvastatin	Zocor	MSD	1	1st	May 1989
Atorvastatin	Lipitor	Pfizer	2	4th	Mar 1997
Pravastatin	Lipostat	Bristol-Myers Squibb	3	2nd	Sep 1990
Rosuvastatin	Crestor	AstraZeneca	4	6th	Mar 2003
Fluvastatin	Lescol	Novartis	5	3rd	Jan 1994
Cerevastatin	Lipobay	Bayer	6	5th	Apr 1997 (withdrawn 2001)

Figure 4.7 shows the diffusion curves for the statin class. Figure 4.8 shows the literature and expert augmented timelines for atorvastatin and rosuvastatin (key events for simvastatin were also incorporated as they were influential on the whole class). Commentaries of the events represented in each timeline are presented in Tables 4.17 to 4.19.

[13] Lovastatin was the first statin, but it was not launched in the UK. Interviewees often discussed worldwide market entry position, making atorvastatin the 5th and rosuvastatin the 7th.

Figure 4.7: Statins - Diffusion Curves

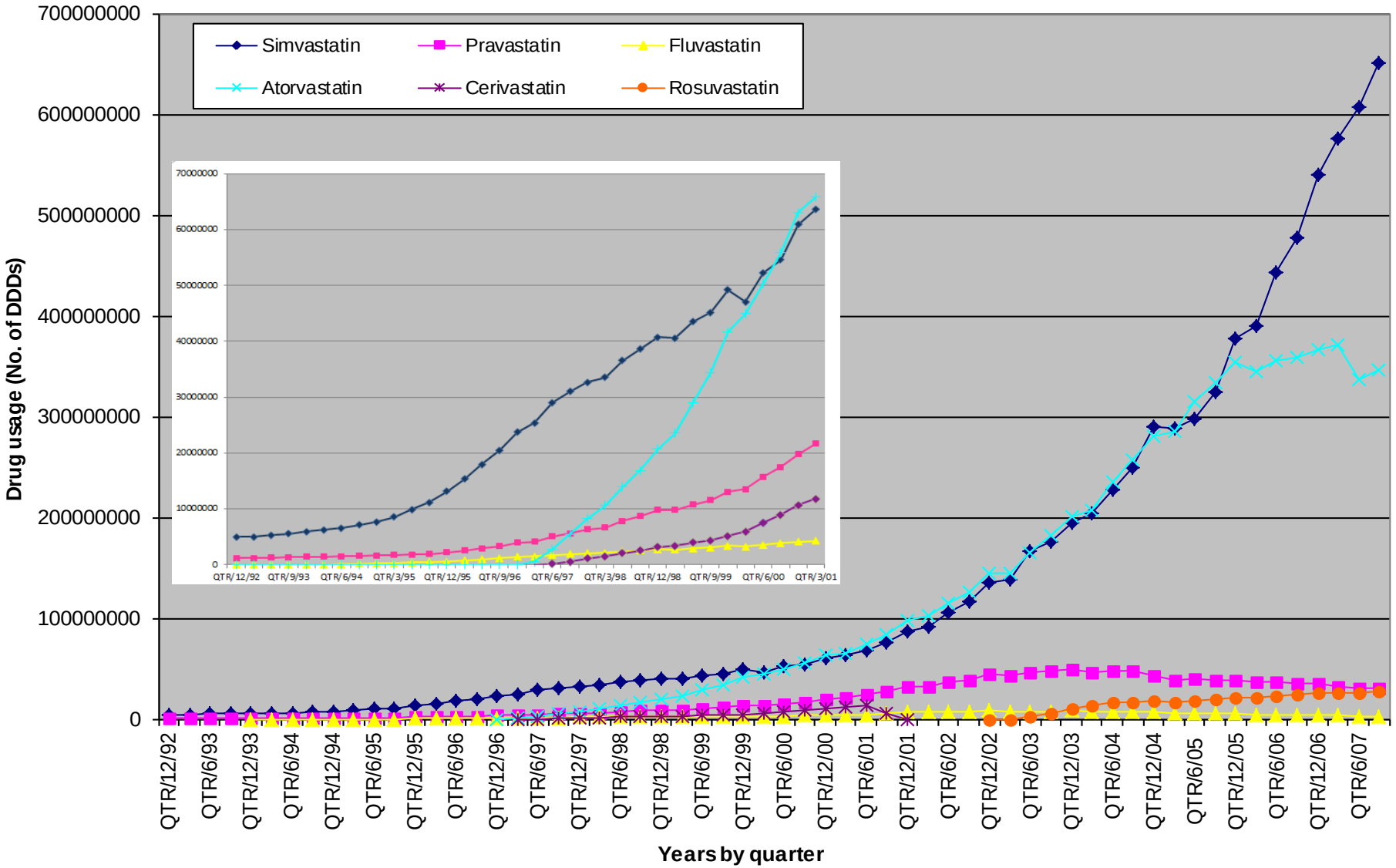
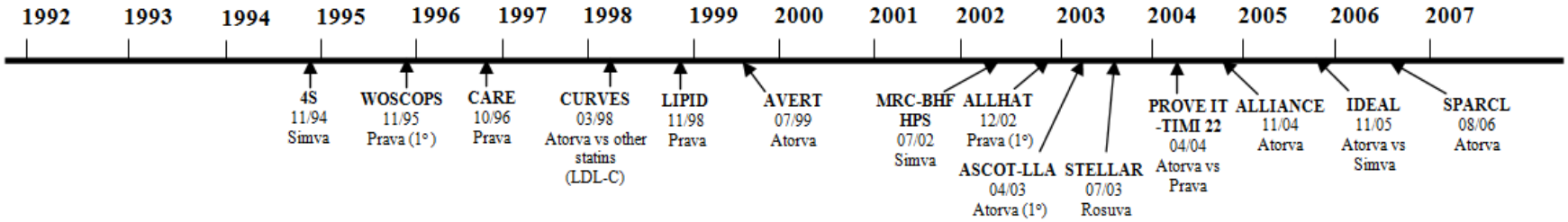
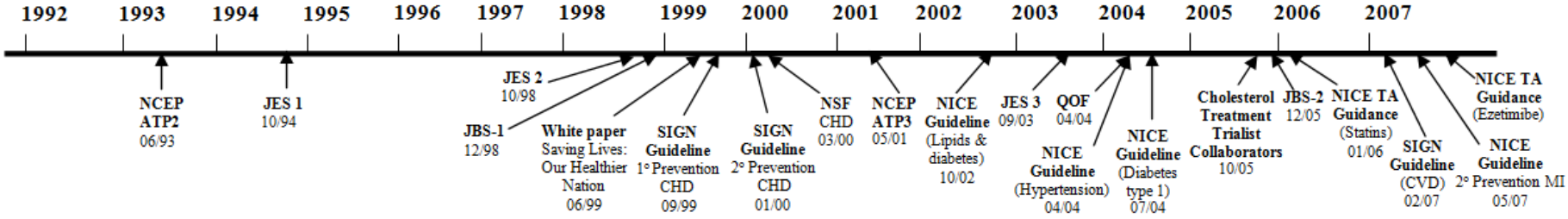


Figure 4.8: Statins - Timeline of Literature and Expert-derived Diffusion Factors
Key: Simva=simvastatin; Atorva=atorvastatin; Rosuva=rosuvastatin; Prava=pravastatin; Cereva=cerevastatin

<u>Primary</u> – Research Trials (See Table 4.17 for commentary) 1° = primary prevention studies (remainder are secondary prevention studies)



<u>Secondary</u> – Guidelines/Reviews/Policy (See Table 4.18 for commentary)



<u>Regulatory/ Licensing (UK)</u> (See Table 4.19 for commentary)

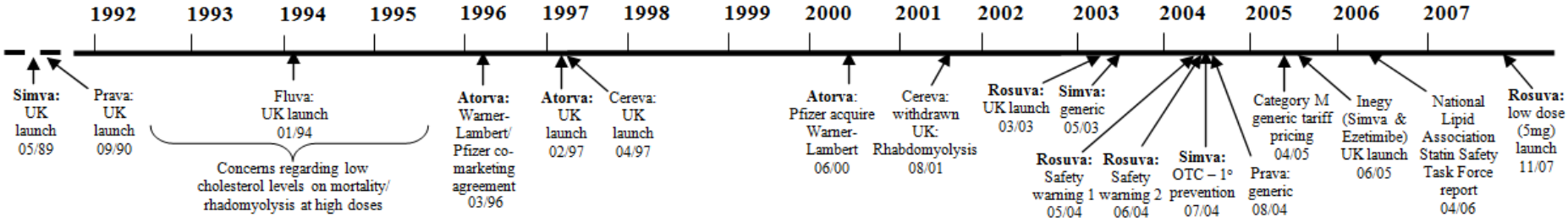


Table 4.17: Statins - Timeline Commentary for Primary Level Evidence

Evidence Summary

The statins are effective in preventing major cardiovascular events and death in both primary and secondary prevention trials in a wide range of at-risk patient groups with a wide range of baseline lipid concentrations (Betteridge, 2011). Despite an extensive evidence suite, several issues relating to trial design raise questions about the extent of clinical utility of some of the studies.

- **Comparative trials:** Comparative effectiveness trials on clinical endpoints have not been done in statins as it requires many years to demonstrate an effect. Head to head studies are therefore based on surrogate LDL-C lowering efficacy. Placebo trials were considered unethical following the landmark statin studies, therefore trials had to at least be conducted against standard of care. As a consequence, later entrants to the market demonstrated benefit in specific patient populations (e.g. acute coronary syndrome; diabetes; the elderly), or of intensive lipid lowering where uncertainty as to statin efficacy remained. While some of these trials appeared comparative, they often used different statin intensities in the two arms (either through a standard dose approach or titrating to a specific LDL-C guideline target) and so are not considered truly head to head studies.

- **Primary endpoints:** In the absence of clinically relevant head to head studies, composite primary endpoints composed of various combinations of cardiovascular events (such as death, MI, unstable angina, coronary revascularisation and stroke) have produced different patient populations, in which different extents of LDL-C reduction have been achieved. This makes it difficult to directly compare statin trial outcomes (Pederson *et al*., 2005). In some studies, primary endpoints have also been affected by control populations also receiving some form of lipid-lowering treatment by the end of the study, compromising the LDL-C lowering differential between the placebo and treatment groups and ultimately the achieved clinical impact.

The trials are separated according to primary and secondary prevention.

Trial	Study drugs	Importance	Study design	Clinical Endpoints[14]	Outcome
SECONDARY PREVENTION OF CORONARY EVENTS – PATIENTS WITH CHD					
4S: Scandinavian Simvastatin Survival Study *Scandinavian Simvastatin Survival Study Group, 1994*	Simvastatin 20-40mg daily vs placebo.	Landmark study - first to demonstrate LDL-C reduction translated to reduced cardiac and all cause mortality.	Randomised, double-blind, multicentre study in 4,444 patients with: Angina or MI; TC: 5.5-8.0mmol/L and mean LDL-C: 4.9mmol/L; 35-70yrs (mean age:	Morbidity and mortality.	Statin therapy reduced the relative risk of : • **Total mortality** by 30% (p<0.001); actual risk reduction (ARR) 3.3% (8.2% vs 11.5% placebo). • **CHD mortality** by 42% (p<0.001); ARR 3.5%. • **CHD events** by 34% (p<0.001); ARR 9% (CHD death, non-fatal definite or probable MI, silent MI, resuscitated cardiac arrest).

[14] Trials incorporating clinically relevant outcomes were included. Exceptions were the first head to head trials based on LDL-C lowering efficacy to include atorvastatin and rosuvastatin, particularly since rosuvastatin had not completed clinical endpoint trials within the time period covered by the diffusion curve.

Trial	Study drugs	Importance	Study design	Clinical Endpoints[14]	Outcome
			58yrs); Av duration: 5.4yrs.		**Lipids:** Mean reductions in TC vs placebo=25%; LDL-C=35%; TG=10%; HDL increase of 8%. Adverse events similar in both groups. One case of rhabdomyolysis in simvastatin arm. Resolved on discontinuation.
CARE **C**holesterol **A**nd **R**ecurrent **E**vents *Sacks et al., 1996*	Pravastatin (40mg) vs placebo.	First study to show statins reduced risk of coronary events even in people with average base-line cholesterol - majority of patients with coronary disease.	Double-blind, randomised, multicentre trial in 4,159 patients with: Prior MI; TC: <6.2mmol/L (mean 5.4mmol/L) and LDL-C: 3.0-4.5mmol/L (mean 3.6mmol/L); 21-75yrs (mean age: 59yrs); Av duration: 5yrs.	Coronary and vascular events, revascularisation.	Reducing LDL-C from average to low levels significantly reduced the number of recurrent coronary events, but did not significantly reduce overall mortality Statin therapy reduced the relative risk of : • **Total mortality** by 9%: non-significant (ns); ARR 0.7%. • **CHD mortality** by 20% (ns); ARR1.1%. • **CHD events** by 24% (p=0.003) ARR; 3% (CHD death, silent or symptomatic non-fatal MI). **Lipids:** TC reduced by 20% vs placebo; LDL-C reduced by 28% (baseline LDL-C of 3.2mmol/L appeared to be an approximate lower boundary for clinical influence on CHD.
CURVES *Jones et al., 1998*	Atorvastatin (10-80mg) Simvastatin (10-40mg) Pravastatin (10-40mg) Lovastatin (20-80mg) Fluvastatin (20-40mg).	First study to compare the lipid lowering efficacy of all marketed statins.	Open label, randomised, multicentre, parallel group trial in 534 patients with: LDL-C: ≥4.2mmol/L, but no CHD; 20-80yrs (mean 55yrs); 8 weeks.	LDL-C reduction.	Atorvastatin 10-40mg produced greater reductions in LDL-C (38% to 51%, respectively; P≤0.01) vs equivalent doses of other statins: Simvastatin (10-40mg) =28 to 41% Pravastatin (10-40mg) = 19 to 34% Fluvastatin (20-40mg) = 17 to 23% Lovastatin (20-40mg) = 29 to 31% Discontinuation of therapy due to adverse events: Atorva <1%; simva 2.2%, prava 1.2%, lova 0% and fluva 4.2%.
LIPID **L**ong-term **I**ntervention with **P**ravastatin in **I**schemic **D**isease *LIPID Study Group, 1998*	Pravastatin (40mg) vs placebo. Secondary prevention in patients with CHD.	First study to show mortality reduction in patients with average base-line cholesterol levels (CARE not designed to detect significant effects on overall mortality or mortality from CHD alone.	Double-blind, randomised, multicentre trial in 9,014 patients with: Angina or MI; TC: 4.0 to 7.0mmol/L and mean LDL-C: 3.9mmol/L; 31-73yrs (mean age: 62yrs); Av duration: 6.1yrs.	Mortality and CV events.	Pravastatin significantly reduced mortality from CHD and overall mortality in patients with a broad range of initial cholesterol levels: Statin therapy reduced the relative risk of : • **Total mortality** by 22% (p<0.001); ARR 3.1%. • **CHD mortality** by 24% (p<0.001); ARR 1.9%. • **CHD events** by 24% (p<0.001); ARR 3.6% (CHD death, silent or symptomatic non-fatal MI). **Lipids:** Mean reductions in TC vs placebo=18% LDL-C=25% TG=11%; increase HDL-C by 5%. No clinically significantly adverse effects between groups.

Trial	Study drugs	Importance	Study design	Clinical Endpoints[14]	Outcome
AVERT **A**torvastatin **VE**rsus **R**evascularization **T**reatment *Pitt et al., 1999*	Atorvastatin (80mg) vs PTCA + usual care. Secondary prevention in patients with CHD.	First clinically relevant endpoint study for atorvastatin – used intensive lipid lowering.	Open-label, randomised, multicentre trial in 341 patients: Requiring angioplasty (stable coronary artery disease); LDL-C: ≥3mmol/L (approximately 80% dyslipidaemic); Mean age: 59yrs Av duration: 18 months.	Ischaemic events.	Intensive LDL-C lowering (to an average 2mmol/L) was at least as effective as angioplasty followed by usual care in reducing incidence of ischaemic events in low-risk patients referred for revascularisation. Intensive treatment with atorvastatin reduced relative risk of: • **Ischemic events** by 36% (p=0.048) ARR 8% (20.9% angioplasty vs 13.4% atorvastatin). • **First event after 6 months** by 46% (ns); ARR 5% (11% angioplasty vs 6% atorvastatin). **Lipids**: Reduction in LDL-C vs usual care=28%.
MRC-BHF HPS (Heart **P**rotection **S**tudy**)** *Heart Protection Study Collaborative Group, 2002*	Simvastatin 40mg daily vs placebo. Secondary prevention in patients with CHD.	Largest ever study conducted in statins (independently funded). Aimed to resolve remaining uncertainties in high risk groups: women; elderly; diabetics, people with low baseline cholesterol; hypertensive patients; prior occlusive non-coronary vascular disease.	Randomised, double-blind, UK study in 20,536 patients with: ± CHD + risk factors (diabetes); TC: ≥3.5mmol/L (mean 5.9mmol/L) and mean LDL-C: 3.4mmol/L; 40-80yrs; Av duration: 5yrs.	Morbidity and mortality.	Statins not only prevent coronary events and coronary revascularisation, but also ischaemic strokes and peripheral vascularisations. Advised initiation of therapy should be guided by estimated risk of suffering any vascular event and not just coronary events. Statin therapy reduced the relative risk of: • **Total mortality** by 13% (p=0.0003); ARR 1.8%. • **CHD mortality** by 17% (p=0.0005); ARR 1.2%. • **Other vascular mortality** by 14% (p=0.07); ARR 0.3%. • **Non-vascular deaths**: Non-significant reduction. • **Major vascular events** reduced by 24% (p=0.0001); ARR 5.4% incorporating reduction in: o **CHD events** by 27% (p<0.0001); ARR 3.1% (non-fatal MI or coronary death). o **strokes** by 25% (p<0.0001); ARR 1.4% (fatal and non-fatal stroke). o **revascularisation** by 24% (p<0.0001); ARR 2.6% (coronary and non-coronary). No threshold cholesterol value below which statin therapy was not associated with benefit. No difference in reports of muscle symptoms (annual excess risk of myopathy was about 0.01%).
STELLAR *Jones et al., 2003*	Rosuvastatin (10-80mg[15]) Atovastatin (10-80mg) Simvastatin (10-80mg) Pravastatin (10-40mg).	First major comparative LDL-C study to also include rosuvastatin against all other marketed statins.	Open-label, randomised, multicentre, parallel group trial in 2,431 patients with: LDL-C: ≥4.2mmol/L to <6.5 mmol/L; >18yrs (mean age: 58yrs); 6 week duration.	LDL-C reduction.	Rosuvastatin (10-40mg) produced greater reductions in LDL-C: 46% to 55%, respectively vs equivalent doses of other statins (p≤0.001): Atorvastatin (10-40mg) 37 to 48%; Simvastatin (10-40mg) 28 to 39%; Pravastatin (10-40mg) 20 to 30%. Pairwise comparisons showed that comparator doses 2 or 4 times higher than rosuvastatin 10 and 20mg did not result in significantly greater LDL-C reductions. Drug tolerability was similar across treatments. No cases of myopathy were detected.

[15] 80mg was not an approved dose of rosuvastatin

Trial	Study drugs	Importance	Study design	Clinical Endpoints[14]	Outcome
PROVE IT-TIMI 22 **PR**avastatin **O**r ator**V**astatin **E**valuation and **I**nfection **T**herapy-**T**hrombolysis **I**n **M**yocardial **I**nfarction 22 *Cannon et al., 2004*	Atorvastatin 80mg vs Pravastatin 40mg.	First head to head trial in statins based on clinically relevant endpoints (not directly head to head as compared different lipid lowering intensities).	Randomised, double-blind, multicentre trial in 4,162 patients with: Acute Coronary Syndrome TC: ≤ 6.2mmol/L (mean 4.7mmol/L) and mean LDL-C: 2.8mmol/L; Mean age: 58yrs; Av duration 2yrs.	Death and major events.	Intensive atorvastatin therapy reduced the relative risk of: • **Time to first occurrence of a component of the primary end point** by 16% (p=0.005) ARR 3.9% (death, MI, unstable angina requiring hospitalisation, coronary revascularisation or stroke). • **Total mortality** by 28% (ns) ARR 1%. **Lipids:** Median LDL-C level: 2.46mmol/L pravastatin vs 1.60mmol/L atorvastatin. Effect seen by 30 days and remained consistent over time (however follow-up time was comparatively short. Not possible to extrapolate findings from acute coronary syndrome to all patients with CHD). Adverse events similar between both groups. No cases of rhadomyolysis.
ALLIANCE **A**ggressive **L**ipid-**L**owering **I**nitiation **A**bates **N**ew **C**ardiac **E**vents *Koren et al., 2004*	Atorvastatin (dose to achieve LDL-C <80mg/dL (2.1mmol/L) or max 80mg vs usual care.	First atorvastatin trial to treat to a target as opposed to using a standard dose.	Open label, randomised, multicentre trial in 2,442 patients with: CHD; TC: mean 5.8mmol/L and LDL-C: 2.8 to 5.2mmol/L on lipid lowering therapy/ 3.4 to 6.5mmol/L not on therapy (mean 3.8mmol/L); 18-75yrs (mean age 61yrs); Av duration 4yrs 3 months.	Major CV events and mortality.	Intensive statin therapy reduced the relative risk of: • **Total mortality** by 5% (ns) ARR 0.5%. • **CHD mortality** by 30% (ns) ARR 1.5%. • **Cardiovascular event** by 13% (p=0.02) ARR 3.5% (cardiac death, non-fatal MI, revascularisation, resuscitated cardiac arrest) – mainly due to fewer non-fatal MI 4.3% vs 7.7% p=0.0002). **Lipids**: Reduction in LDL-C vs usual care = 11%; NCEP goals of <2.6mmol/L more likely to be met with atorvastatin (72.4% vs 40%).
IDEAL **I**ncremental **D**ecrease in **E**ndpoints through **A**ggressive **L**ipid lowering *Pederson et al., 2005*	Atorvastatin 80mg vs Simvastatin (20-40mg).	First comparative trial involving simvastatin. - compared different lipid lowering intensities but no difference observed in major coronary events.	Randomised, open-label, blinded endpoint, multicentre trial in 8,888 patients with: CHD (stable), prior MI; TC varied: mean 5.1mmol/L and LDL-C varied: mean 3.2mmol/L; ≤80yrs (mean age 62yrs); Av duration 4.8yrs.	Coronary and vascular death and CV events.	Atorvastatin and simvastatin were indistinguishable in the 'major coronary events' endpoint (10.4% simvastatin vs 9.3% atorvastatin (p=0.07 ns). No differences in cardiovascular and all-cause mortality, but there was a reduced risk of other composite secondary end points and nonfatal acute MI. No difference in serious adverse events (myopathy and rhabdomyolysis rare in both groups). Elevated liver enzymes more common in atorvastatin group.
SPARCL **S**troke **P**revention by **A**ggressive **R**eduction in **C**holesterol **L**evels *SPARCL Investigators, 2006*	Atorva (80mg) vs placebo. Secondary prevention of **stroke** (primary	Market development - new indication of preventive management in stroke – possible to conduct as a placebo-controlled trial as new indication	Randomised, double-blind, multicentre trial in 4,731 patients with: Prior stroke or TIA, no known CHD; TC: mean 5.5mmol/L and LDL-C: 2.6 to 4.9mmol/L:	Stroke.	Atorvastatin moderately reduced the overall incidence of subsequent stoke in people with a recent history of stroke or TIA, but without known CHD. Statin therapy reduced the relative risk of : • **Fatal or non-fatal stroke** by 15% (p=0.05) ARR 1.9%. • **Total mortality** by 2% (ns) ARR 0.2%. 5 year ARR of major cardiovascular event=3.5% (p=0.002). Contrasted with results of Heart Protection Study, which found no reduction in the risk

Trial	Study drugs	Importance	Study design	Clinical Endpoints[14]	Outcome
	prevention of CHD).	and therefore was not considered unethical.	(mean 3.5mmol/L); ≥18yrs (mean 63yrs); Av duration 4.9yrs.		of stroke among patients with prior cerebrovascular disease (potentially due to lower dose statin and enrolment at a later point after the incident than SPARCL). **Lipids:** Mean LDL-C reduced to 1.89mmol/L in the atorvastatin group as compared with 3.3mmol/L in placebo (p<0.001). Serious adverse events were similar between both groups. Elevated liver enzymes more common in atorvastatin group. Small increase in haemorrhagic stroke.
PRIMARY PREVENTION OF CORONARY EVENTS – PATIENTS WITHOUT CHD					
WOSCOPS **W**est **O**f **S**cotland **CO**ronary **P**revention **S**tudy *Shepherd et al., 1995*	Pravastatin (40mg) vs placebo.	First prevention study - statins could prevent first time heart attacks and angina and reduce mortality in otherwise healthy men with hypercholesterolaemia (pre-heart attack patients) – much bigger market than post-heart attack.	Randomised, double blind, UK multicentre trial in 6,595 patients with: TC: mean 7.0mmol/L and LDL-C: mean 5mmol/L (no history of MI); 45-64yrs (mean age 55 yrs); Av duration 4.9yrs.	CHD death and non-fatal MI.	Pravastatin significantly reduced incidence of MI and death from cardiovascular causes in men with moderate hypercholesterolaemia and no history of MI. Statin therapy reduced the relative risk of : • **Non-fatal MI or death from CHD** by 31% (p<0.001); ARR 2.4%. • **Total mortality** by 22% (p=0.051) ARR 0.9%. • **Cardiovascular mortality** by 32% (p=0.033) ARR 0.7%. No excess deaths in pravastatin group - alleviated concerns that statins increased deaths from non-cardiovascular causes. **Lipids:** TC reduced by 20%; LDL-C by 26% (no change with placebo). American AFCAPS/TexCAPS study (Downs *et al*., 1998) using lovastatin in a 'healthy' population, supported results of WOSCOPS.
ALLHAT-LLT **A**ntihypertensive and **L**ipid-**L**owering treatment to prevent **H**eart **A**ttack **T**rial; **L**ipid-**L**owering **T**rial *ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002*	Pravastatin 40mg vs usual care (both arms with anti-hypertensives).	Major negative study for statins in primary prevention.	Randomised, open-label, multicentre trial in 10,335 patients with: Hypertension (well-controlled) and ≥1 CHD risk factors; TC: mean 5.8mmol/L and LDL-C: 3.1 to 4.9mmol/L (mean 3.8mmol/L); ≥55yrs (mean age 66yrs); Av duration 4.8yrs	All cause and CHD mortality.	All clinical endpoint results were non-significant. Results suspected to be due to the modest differential in TC (9.6%) and LDL-C (16.7%) between pravastatin and usual care compared with other major statin trials. Almost one third of usual care patients began taking a lipid lowering drug during the study, contributing to the non-significant LDL-C differences. Study became detrimental to pravastatin's continued diffusion.

Trial	Study drugs	Importance	Study design	Clinical Endpoints[14]	Outcome
ASCOT-LLA **A**nglo-**S**candinavian **C**ardiac **O**utcomes **T**rial – **L**ipid **L**owering **A**rm *Sever et al., 2003*	Atorvastatin 10mg vs placebo (both arms with anti-hypertensives).	First study of atorvastatin based on a mortality clinical endpoint and in primary prevention.	Randomised, double-blind, multicentre trial in 10,305 patients with: Hypertension and ≥3 CHD risk factors; TC: ≤6.5mmol/L (mean 5.5mmol/L) and LDL-C: mean 3.4mmol/L; 40-79yrs (mean age 63yrs); Av duration 5yrs (study ended early after 3.3yrs due to observed benefit in treatment arm).	CHD death and non-fatal MI.	Statin therapy reduced the relative risk of : • **CHD mortality and non-fatal MI** by 36% (p=0.0005); ARR 1.1%, • **Total mortality** by 12% (ns); ARR 0.5% • **Cardiovascular mortality by** 12% (p=0.051) ARR 0.2% • **Fatal and non-fatal stroke** by 27% (p=0.024). ARR 0.7% **Lipids:** Atorvastatin lowered TC by 1.1mmol/L after 3yrs. No significant adverse effects.

Table 4.18: Statins - Timeline Commentary for Secondary Level Evidence and Policy

Despite the emphasis placed on lipid goals in guidelines, no trials have specifically evaluated the relative and absolute benefits of lowering cholesterol to specific TC and LDL-C targets in relation to clinical events. Instead they have used standard doses and the targets have been derived through extrapolation of benefits in major trials (British Cardiac Society *et al*., 2005).

Secondary Evidence and Policy	Description
NCEP (National Cholesterol Education Program) guidelines (USA) - Adult Treatment Panel (ATP) I (Jan 1988), **II** (Jun 1993), **III** (May 2001)	USA produced the first major clinical guidelines in relation to CHD risk reduction through lowering high blood cholesterol following the publication of the National Institute of Health Lipid Research Clinics-Coronary Primary Prevention Trial (LRC-CPPT) (Lipid Research Clinics Program, 1984). **ATP I (1988)**: identified LDL-C as the primary target of therapy, emphasising clinical management of patients with higher levels of LDL-C. Statins, as new drugs, were advised to be used with caution. **ATP II (1993)**: CHD risk stratification refined to 3 categories: i) patients with CHD, ii) patients without CHD who have ≥2 risk factors, and iii) patients without CHD who have <2 risk factors. The LDL-C target for patients with CHD became more stringent ≤100mg/dL (2.6mmol/L). Statins became classified as major drugs. **ATP III (2001)**: included in the highest-risk category i) not only patients with CHD but also patients with CHD risk equivalents (other atherosclerotic disease, diabetes, and a calculated 10-year risk for CHD >20%). Category ii) split into 2 groups - calculated 10-year risk of 10–20% or <10%. Lowest risk category iii) remained the same. Result was to increase number of people with LDL-C goal of 2.6mmol/L (estimates suggested the guideline tripled the number of people with cholesterol levels classified as abnormal).
JES (Joint European Societies) Guidelines: **JES1**: Pyorala *et al*., 1994; **JES2**: Wood *et al*., 1998b; **JES3**: de Backer *et al*., 2003	**JES (1994):** TC≤5mmol/L ideal. **JES 2 (1998):** TC<5mmol/L and an LDL-C goal of 3mmol/L in patients with established CHD, other atherosclerotic disease, or high absolute risk. **JES 3 (2003):** In general TC should be below 5mmol/L and LDL-C should be below 3mmol/L. In patients with clinically established CVD and patients with diabetes the treatment goal should be TC<4.5mmol/L and LDL-C<2.5mmol/L.
JBS (Joint British Societies) guidelines; **JBS1** - Wood *et al*., 1998a; British Cardiac Society *et al*., 2000 **JBS 2** British Cardiac Society *et al*., 2005	**JBS1 (1998)**: Defined TC target as 5mmol/L and LDL-C target as 3mmol/L. Also put forward proposals for risk assessment and management in the asymptomatic population without CVD (published initially in December 1998 (Wood *et al*., 1998) and separately by the British Cardiac Society in the BMJ in March 2000 to coincide with the release of the NSF for CHD). **JBS2 (2005)**: Set lower optimal TC lipid targets as 4mmol/l and LDL-C targets as 2mmol/l, or a 25% reduction in TC and a 30% reduction in LDL-C whichever achieves the lowest absolute value.
White paper 'Saving Lives: Our Healthier Nation' (DH, 1999a)	Government commitment to reduce the death rate from CHD, stroke and related diseases amongst people under 75 years by at least two-fifths by 2010 to save a total of 200,000 lives. The National Service Framework in CHD was intended to help achieve the ultimate target as set out in the White Paper.
SIGN Guideline No. 40 –Primary prevention of CHD, 1999	A patient should be considered for lipid lowering drug therapy following lifestyle measures and other appropriate interventions (for at least 3months) when TC is 5.0mmol/L and the 10 year risk of a major coronary event is 30% using the Joint British Societies Coronary Risk Prediction Chart For primary prevention of coronary heart disease. Statins (pravastatin and simvastatin) drugs of first choice for lowering lipids.
SIGN Guideline No. 41 – Secondary prevention of CHD, 2000	If TC is 6.0mmol/L, drug therapy to reduce cholesterol should be initiated, titrated as necessary to reduce TC to <5.0mmol/L. Pravastatin and simvastatin are the drugs of choice for lipid lowering for secondary prevention of coronary heart disease following MI.
NSF-CHD (National Service Framework for Coronary Heart Disease) (DH, 2000)	Set standards for the prevention and treatment of CHD in people with established CHD, and apparently healthy individuals at high multifactorial risk of developing CHD. Recommended the JBS1 coronary risk prediction charts for total CHD risk estimation in an asymptomatic population, indicating statins be targeted only at those asymptomatic individuals with a total CHD risk of ≥30% (JBS1 recommended intervention at lower risk threshold of ≥15%) Defined targets of TC ≤5mmol/L and LDL-C ≤ 3mmol/L or a 30% LDL-C reduction as target levels. The increase in provision of statins to patients was seen as one of the most important markers of progress on the National Service Framework (NSF) for CHD.

Secondary Evidence and Policy	Description
NICE Guideline – Management of type 2 diabetes: management of blood pressure and blood lipids Inherited Guideline H, 2002c	Recommended that in people with type 2 diabetes and consistently high lipid levels, the goal with drug therapy was to reduce TC to <5mmol/L or to 75-80% of the level before treatment, whichever is lower; or reduce LDL-C to <3mmol/L or to 70% of the level before treatment, whichever is lower.
QOF, Quality and Outcomes Framework, 2004	The QOF of the General Medical Services contract, which offers incentive payments linked to several prescribing targets, provided an added incentive for GPs to regularly monitor and review patients with CVD or who were at high risk of CVD. QOF indicators for CHD, stroke and diabetes used target TC of ≤5mmol/L.
NICE Guideline – Hypertension CG18, 2004b; update 2006	Lipid-lowering therapy should be considered alongside the use of antihypertensive therapy in patients at raised cardiovascular risk. Did not specifically state statins. No change to this reference in update.
NICE Guideline – Diabetes type 1 CG15 2004a	A standard dose of a statin should be recommended for adults in the highest risk and moderately high-risk groups.
Cholesterol Treatment Trialist Collaborators. Baigent *et al*., 2005	Influential systematic review: Included 14 randomised trials, involving over 8,000 deaths, 14,000 major vascular events, and 5,000 cancers among 90,056 participants. Showed statin therapy reduced the incidence of major coronary events and that relative risk reduction was related to the absolute reduction in LDL-C levels from baseline, but largely unrelated to the initial lipid profile or other presenting characteristics.
NICE TA (Technology Appraisal) Guidance - Statins for the prevention of cardiovascular events TA 94, 2006	Once the decision has been made to prescribe a statin, therapy should be initiated with a drug with a low acquisition cost (taking onto account required daily dose and product price per dose). Rosuvastatin assessed on surrogate endpoints. While there was no data to suggest the superiority of one statin over all the others in reducing cardiovascular events (comparative studies on clinical events were unavailable at the time of the TA), in view of the substantial price reduction of generic simvastatin, prescribing formularies used the guidance to support the preferential use of simvastatin.
SIGN Guideline No. 97 – Risk estimation/prevention of CVD , 2007	Adults over the age of 40 years who are assessed as having a 10 year risk of having a first cardiovascular event ≥20% should be considered for treatment with simvastatin 40mg/day. Patients with established symptomatic atherosclerotic CVD should be considered for more intensive statin therapy. In diabetic patients with mixed dyslipidaemia and elevated LDL-C, guideline supported prescribing statins to people with established CVD and for individuals with a CVD risk as low as 10% over ten years or with baseline cholesterol levels of over 7.5mmol/L.
NICE Guideline - MI: secondary prevention MI CG48, 2007a	Statin therapy is recommended for adults with clinical evidence of cardiovascular disease in line with 'Statins for the prevention of cardiovascular events' (NICE technology appraisal guidance 94). After an MI, all patients should be offered treatment with a statin as soon as possible.
NICE TA (Technology Appraisal) Guidance – Ezetimibe for the treatment of hypercholesterolaemia - TA 132, 2007b	Guidance recommended that ezetimibe monotherapy be given to people in whom a statin is contraindicated, or co-administered with a person's usual statin rather than changing to a new statin when cholesterol levels are not low enough despite increasing the dose of the statin.

Table 4.19: Statins - Timeline Commentary for Safety and Regulatory Events

Note: Not all licensing events that appear on the timeline are represented in the table below. Ony those events that required additional context are presented.

Events	Description
Simvastatin launch May 1989	Simvastatin was launched into a cautious environment. While it was known that atherosclerosis was a major cause of cardiovascular mortality and morbidity, the role of LDL-C in reducing overall mortality was controversial (Davey Smith and Pekkanen, 1992; Oliver, 1992). Trials had shown that lowering LDL-C through various mechanisms (diet, drugs such as fibrates and bile acid sequestrants [cholestyramine, cholestipol], or surgery [partial ileal bypass surgery]) reduced CHD event rates, but there was no impact on overall mortality (Lipid Research Clinics Program, 1984; Buchwald *et al*., 1990). The modest reductions in TC achieved (approximately 10%) and the correspondingly modest reductions in CHD mortality were offset by small increases in non-cardiovascular mortality reductions (Gordon, 1995). The statins however, lowered TC by 20% or more, which provided the opportunity to effectively assess the overall benefits and risks of cholesterol lowering.
Concerns regarding low cholesterol levels on mortality/rhabdomyolysis at high doses. Early to mid 1990s	Despite the sea change in behaviour towards statin use caused by the 4S study in 1994, concerns remained about statin-induced rhabdomyolysis from high doses; and even the prospect of increased mortality related to persistently low lipid levels, which were making many clinicians wary of aggressive treatment (Anderson *et al*., 1987; Behar *et al*., 1997; Davey Smith and Pekkanen, 1992). Studies, such as CARE were also suggesting a potential LDL-C threshold beyond which no further statin-derived benefit could be gained which impacted on statins claiming greater potency.
Warner Lambert/ Pfizer co-marketing agreement Mar 1996	Atorvastatin was originally developed by Parke-Davis, a division of Warner-Lambert. In 1996, just ahead of atorvastatin's launch they partnered with Pfizer to co-market the drug to utilise their marketing power.
Atorvastatin launch Feb 1997	By the time atorvastatin was launched, the relationship between LDL-C reduction and mortality had been established which enabled atorvastatin to demonstrate superiority in comparative studies against competitor statins on the basis of LDL-C lowering ability alone. A strategy based on greater potency however, was risky against the backdrop of potency-related concerns. Approval of doses up to 80mg however, gave the perception that the starting dose of 10mg, (which was below other available statins) was very safe. Atorvastatin came with a lower pricing strategy than simvastatin.
Pfizer acquire Warner-Lambert Jun 2000	Pfizer acquired Warner-Lambert in June 2000, gaining total control of atorvastatin and creating the world's second largest pharmaceutical company, after GSK.
Cerevastatin withdrawn Aug 2001	Bayer voluntarily withdrew cerevastatin following reports of 52 deaths worldwide from rhabdomyolysis (many of these patients were also prescribed fibrates). The entire class came under scrutiny, but other marketed statins were able to distance themselves, largely due to the vast amount of safety data accumulated during large scale clinical trials. The simvastatin Heart Protection Study a year later was reassuring to clinicians due to its scale, but made it difficult to make the case to use any other statins first-line.
Rosuvastatin UK launch Mar 2003	Rosuvastatin was the most potent statin on the market following cerevastatin's withdrawal and was labelled a 'super-statin'. Pfizer's message of 'lower is better' had primed the market for rosuvastatin's introduction. Its increased potency meant it was less expensive than its competitors at equivalent efficacy doses.
Simvastatin – generic May 2003	As simvastatin 40mg could reduce LDL-C by around the same amount as 10mg or 20mg atorvastatin (i.e. 30-40%, which is in line with most guideline targets), prescribing policies were adopted to switch patients from these doses of atorvastatin to generic simvastatin. There was concern however, that some patients who required more intensive therapy were being inappropriately switched.
Rosuvastatin safety warning 1 May 2004	A year after launch, rosuvastatin was linked to the same safety issues that had been responsible for cerevastatin's withdrawal (four cases of rhabdomyolysis and one case of renal impairment secondary to myositis (muscle inflammation) in patients initiated on doses of rosuvastatin greater than that recommended) (MHRA, 2004b). This prompted the release of a 'Dear Doctor' letter reminding health professionals of the importance of starting patients on the lowest dose (10mg).
Rosuvastatin safety warning 2 Jun 2004	Within a month of the first safety alert, a second 'Dear Dr' letter was released that included specific prescribing advice that i) all patients must start on the initial dose of 10mg rosuvastatin once daily and should only be increased to 20mg if considered necessary after a four week trial of 10 mg, ii) the 40mg dose is contraindicated in patients with predisposing risk factors for muscle toxicity and iii) specialist supervision (with international normalised ratio [INR] monitoring) is recommended when the 40mg dose is given. The 40mg dose should only be necessary for the minority of patients with severe hypercholesterolaemia at high cardiovascular risk.

Events	Description
Simvastatin OTC (over the counter) - primary prevention Jul 2004	Pharmacists were able to provide low dose simvastatin (10mg) to people with moderate CVD risk (10-15% 10 year risk). This included all men aged 55 years or older without other risk factors; men aged 45-54 or women 55 years and older with one or more risk factors (smoker; obese; family history of premature CHD; or of Asian ethnicity).
Category M generic tariff pricing Arp 2005	The price of generic simvastatin remained comparable with branded statins until May 2005 following the introduction of Category M generic tariff pricing. The significant price drop meant that manufactures of branded statins could not present an argument at low doses (cost savings were estimated to be near £250 million), but in those patients requiring intensive lipid lowering, simvastatin even at its highest recommended dose could not achieve the same degree of lipid lowering as the higher doses of atorvastatin and rosuvastatin. Enabled a differentiation strategy to be adopted based on potency, with the branded statins competing for niche patient groups (Pfizer used their extensive safety data as the basis of their argument to not switch from atorvastatin, in the knowledge it would take many years for AstraZeneca to develop a similar evidence suite).
Inergy UK launch Jun 2005	Inergy is a combination formulation of simvastatin and ezetimibe. Ezetimibe reduces LDL-C by an average of 18% and can be used in addition to statins to enhance lipid lowering efficacy due to its complementary action. As Ezetimibe was also available as a separate drug (Zetia, Schering Plough – launched April 2003), it was often used in combination with generic simvastatin to enhance its lipid lowering efficacy at a reduced cost compared with Inegy. Even with reductions to the price of generic simvastatin, the additional cost of ezetimibe made this combination more expensive than high dose monotherapy with either atorvastatin or rosuvastatin.
National Lipid Association Statin Safety Task Force, Jun 2006 McKenney *et al*., 2006	A post-marketing analysis of safety reports to the Food and Drugs Administration (FDA) during the first year found patients taking rosuvastatin were eight times more likely to develop rhabdomyolysis, nephropathy, renal failure or proteinuria than patients taking pravastatin and 6.5 times more likely to develop those complications than patients taking atorvastatin (Alsheikh-Ali *et al*., 2005). Fearing concerns that rosuvastatin would be reserved as a second-line therapy after failure of the more established statins, a series of safety reports including the National Lipid Association Statin Safety Task Force Report supported by AstraZeneca, were published assessing data from several hundred thousand patients, concluding that all currently marketed statins have a similar low risk of serious adverse events (Shepherd *et al*., 2004).
Rosuvastatin low dose (5mg) Nov 2007	A new lower dose of 5mg was launched, still capable of lowering LDL-C by around 40% in patients predisposed to myopathy (elderly, renally impaired) with the aim of reducing safety concerns (Teramoto and Watkins, 2005).

4.6. Chapter comment

This chapter presented the results of the case study specific components of the research. An extensive array of events were identified for each case study from the literature and prioritised with clinical expert input. Drug-specific unannotated diffusion curves provided the basis for discussion with interviewees. The timelines were not supplied to interviewees, but provided background preparatory information and were used as a triangulation source to be used alongside the Industry accounts.

CHAPTER 5

THEMATIC ANALYSIS OF INDUSTRY INTERVIEWS

5.1. Introduction

This chapter is a presentation of the 10 themes inductively derived across all case studies from the interviews with the pharmaceutical industry. The data is presented across all case studies by theme and subtheme with elucidation of the inter-connected relationships to construct an interpreted reality of influential diffusion factors from an Industry perspective.

The thematic analysis is entirely a presentation of my inferences from the content of the views expressed by Industry respondents. Each theme is augmented by supporting quotes, with the key sections of the text highlighted in bold font. To enhance transparency, the majority of the corpus of interview material is presented. Reasons for not including a quote were predominantly due to duplication of a concept, in which case the best exemplifying quote was selected.

This chapter is presented according to the final framework categories, but their iterative development is documented in Appendix 11.

5.2. Thematic Framework

1. **CLINICAL NEED**

   1.1. Discontent with current therapies

   1.2. Innovation inertia: Desire for something new in a stagnating field

   1.3. Vocational need to alleviate distress

   1.4. Disparity between clinician and patient–driven needs

   1.5. Need to satisfy innovator pursuit

   1.6. Industry response to unmet clinical need

2. CLINICIAN/PATIENT EXPERIENCE (EFFECTIVENESS)

   2.1. Subjective evaluation based on personal clinical experience

   2.2. Clinician-patient interaction

   2.3. Inappropriate drug use

      2.3.1. Distorted experience

      2.3.2. Safety warnings/concerns

   2.4. Patient insight

   2.5. Industry response to experiential barriers

3. CLINICAL EVIDENCE (EFFICACY)

   3.1. 'Marketing' evidence

   3.2. Impact of clinical evidence

      3.2.1. Trial design

         3.2.1.1. Functional versatility of evidence

         3.2.1.2. Novel trial perspective

      3.2.2. Evidence translation: Relevance/limitation of trial outcomes

         3.2.2.1. Head to head comparisons

         3.2.2.2. Surrogate markers versus clinically relevant outcomes

      3.2.3. Temporal impact of evidence

      3.2.4. Journal quality/Publication control

4. HEALTH SERVICE/POLICY ENVIRONMENTS

   4.1. Health policy environment

      4.1.1. Political priorities

         4.1.1.1. Favourable policy environment

         4.1.1.2. Adverse policy environment

   4.2. Independent guidance/guidelines

      4.2.1. Differentiation

      4.2.2. Perceived importance/ strength of message

      4.2.3. Timeliness

   4.3. Health service environment

      4.3.1. Clinical priorities

      4.3.2. Clinical setting of disease management (specialist/non-specialist)

   4.4. Industry response to environmental barriers

5. ADOPTER ATTITUDE

   5.1. Clinician conservatism

   5.2. Disease perception

   5.3. Non-specialist risk mitigation

   5.4. Industry response to attitude barriers

6. **COMMUNICATING RELATIVE ADVANTAGE**

6.1. Differentiating relative advantage

6.1.1. Real versus perceived benefits

6.1.2. Market entry position

6.1.3. Perception of brand identity

6.2. Conveying relative advantage

6.2.1. Simplicity/ clarity of message

6.2.1.1. Tailoring the message to adopter needs

6.2.1.2. Targeting the message

6.2.2. Product awareness (advertising)

6.2.2.1. Managing expectations

6.2.3. Product justification (representative detailing)

6.2.3.1. Competitor objection handling

7. MARKET DEVELOPMENT

7.1. Market research

7.2. Raising disease awareness

7.2.1. Patient group role

7.2.2. Public figure/celebrity endorsement

7.2.3. Media role

7.3. Market leadership

7.3.1. Corporate philanthropy: subsidy of health services

7.4. Research: new formulations/new indications

7.5. Dispensing/supply issues

8. KEY OPINION LEADERS (KOLs)

8.1. Early engagement/collaboration

8.2. Hierarchical cascade of influence/peer credibility

8.3. Advancing the field through collegiate agreement

9. COMPANY CULTURAL HERITAGE/ PERCEPTION

9.1. Cultural influence on company perception

9.2. Culture determining company priorities

10. PRICING

10.1. Price setting

10.2. Price perception

5.3. Thematic Analysis

1. CLINICAL NEED (Clinician/patient)

An analysis of respondent views indicated that clinical need is a somewhat multi-stranded concept, with each aspect rooted in the desire of clinicians or patients to find solutions to clinical problems, which cannot be addressed with existing technology. This was a theme raised by all respondents during their discussions as they considered unmet clinical need is a powerful driver of diffusion on which many other influences depend; new drugs that meet genuine needs were considered to face few barriers to diffusion. Industry respondents conceptualised various manifestations of clinical need.

*It's **not necessarily evidence as such, but it was meeting clinical need**. So again, a clinical need is a big driver in terms of shifting and kicking the line (G1.2).*

*How do you actually make sure that, when you're communicating your product you're **talking about things that the doctors are interested in and are going to switch the doctor on** in terms of **when they're making that decision that it's your drug that they use versus the other. So you have to understand the drivers to prescribing**, whether it be efficacy, safety, patient convenience. And it's **different for every market** (G1.2).*

1.1. Discontent with Current Therapies

The consensus Industry view was that discontent with current therapy drives clinical need due to deficiencies within existing classes of therapies such as the need for greater efficacy, fewer side effects, or an improved formulation to increase patient compliance. An inference that can be taken from these views is that once this need has been met by an innovation, further clinical need may then result from subtle inadequacies within a class. For example, the BPs were believed to effectively fill a 'pharmacological void' as no treatments existed beyond calcium and vitamin D supplements borne out of a perception that osteoporosis was an accepted condition of

ageing rather than a preventable disease (see Theme 5: Adopter Attitude: subtheme 5.2: Disease perception). Within the class, respondents indicated additional need developed from patients' discontent with the complicated administration protocols necessary to reduce the risk of adverse side effects. A complex regime therefore did not appear to fit comfortably with the physical needs of an ageing patient group.

An analysis of respondents' views demonstrated that defining clinical need is not necessarily limited to the realms of clinicians. With patients becoming increasingly informed about their conditions, comes the prospect of changing expectations around what treatments should be available. Respondents highlighted across all case studies how patient dissatisfaction with therapies can potentially lead to compliance issues, which has significant implications for diffusion of drugs, particularly for chronic conditions. Improving patient compliance through new formulations was viewed by respondents as a way of driving diffusion, even in the absence of improved effectiveness.

> *I think we genuinely **underestimated the grumbling amount of discontent about daily products**…and I think it's **a mistake we probably would learn from** (CS1.2).*
>
> *It's a breakthrough because you're actually **hitting a major innovation for the category**. Suddenly you're offering a **product that is offering a much easier compliance**, and you're offering this into a background **where doctors are saying 'I would use them, but I keep getting people that don't want to take them in the way that they're meant to take them so I'm not'. Patients were saying 'I don't like it this way'** (CS1.1).*

Clinical need for AAs was attributed to the undesirable side effect profiles of their predecessors. Similar issues in the PDE5 inhibitor case were believed to be the driver for the need for alternatives.

There are relatively few drugs that completely change the dynamic of a market place. I mean really, ***the options were pretty grim before Viagra*** *you know, there was* ***surgical or it involved injections****…and those sorts of things. Suddenly* ***here was this rather elegant tablet…so the unmet need was there****, and of course with the publicity, that led to that amazing take off (CS3.1).*

1.2. Innovation Inertia: Desire for Something New

Respondents indicated that lack of innovation in a particular clinical field over a prolonged period inducing clinical frustration can accelerate the diffusion of a new drug. The assertion therefore is that innovation inertia heightens anticipation and expectations amongst adopters, but this could potentially be at the expense of rigorous scrutiny if the need is great enough.

The first ***atypical antipsychotic was actually quite eagerly awaited*** *because before you had conventional antipsychotics, and they've been around since the 1950s, and there* ***hadn't really been a great move in terms of medication since the 1950s, and although those drugs were quite good on efficacy*** *so that they were reasonable at controlling the symptoms,* ***side effects were a major issue****, particularly what we call extra pyramidal side effects which is basically sort of shaking of the body, which is quite marked with the older drugs, so I think* ***from a psychiatrist's point of view they were actually quite excited to have a new class of drug*** *in the atypical antipsychotics with Risperdal (risperidone) really being the first (CS2.1).*

The thing that really differentiates Zyprexa (olanzapine) was just the sheer level of interest by physicians*. It wasn't a case of, you know, there was* ***no push*** *of the drug onto the market necessary, there was a* ***real pull for it****. I've* ***never known demand for a drug like it****. You know, even pre-launch, when we weren't doing anything promotionally, obviously, because we weren't allowed to, there was a real demand for it., and the* ***treatment of schizophrenia was a pharmacological museum up until that point****. The main stay of treatment in hospitals up and down the UK were drugs which were first licensed in the 50's and 60's.. And it had* ***been so long since a real breakthrough*** *I think, you know, the* ***pent up demand was unprecedented****. We were positively surprised by the enthusiasm which was met by Zyprexa. Very positively surprised. It did exceed our expectations (CS2.4).*

1.3. Vocational Need to Alleviate Distress

The ability to alleviate a patient's distress appears to underpin clinical need in that respondents indicated they believe conditions with overt symptoms, such as schizophrenia, can create a heightened sense of need to use something that may achieve a response over and above current treatments. This in itself can be a powerful driver behind the use of a new drug. Analysis of views on this topic,

suggests respondents believe there is an emotive element that underpins this form of clinical need in that it is closely related to how traumatic the symptoms of the disease are, highlighting a linkage between clinical need and clinician experience (see Theme 2: Clinician/patient experience). The suggestion that witnessing a positive impact of treatment will also reinforce prescribing behaviour to perpetuate continued use is supportive of this view.

*No matter what product you launch **you've got to know what the needs of your patients and your prescribers are**. For this one it's **so traumatic**, you know, we do a lot of customer research prior to launch and after launch around what the goals of treatment are, and for the prescriber their **number one goal of treatment is to protect against relapse and that's because just what they see the patient go through** and how hard it is to build that trusting relationship that they need with the patient once they have relapsed (CS2.2).*

*I think also a **recognition** of what really helps, **what gains more empathy with the patient and with the doctor.** Here [immediately post-launch] you **can't sell a drug that isn't efficacious**, it's got to work. The **doctor wants to know it works**. Does it do something? You know. **Once they've got used to the idea** 'I know this thing works, I know it's a good drug' what they want to do is **focus on 'there's real benefits for my patients** here. This is **making me feel good** that I'm giving them the best' (CS1.3)*

1.4. Disparity Between Clinician and Patient-driven Needs

A perspective elucidated from analysis of respondents' views, predominantly from the PDE5 inhibitor case study but touched upon in some of the other cases, was the concept that there is a relationship between the physical manifestations of a disease and which of the different user group's needs then take priority, be that patients or clinicians. There was a belief amongst respondents that in symptomatic conditions, diffusion was largely patient-driven, with the needs of clinicians prevailing when outcomes were related more to explicit clinical measures. The inference is that while they are not mutually exclusive, they can be quite distinct and diffusion can depend on whose priorities prevail.

*We **came into a market that was massively**...or we thought **was massively satisfied in the mind of the physician**, why would they do anything else? You know, **what's driven this** a lot has been the **patients coming back and actually saying that's really good** (CS3.2).*

So if you take the asthma market, it's very patient-orientated. So there's a ***big patient drive to basically support the patients, meet the patient's needs, be very patient friendly, because it's symptomatic, the patients obviously notice it*** *and you have to get them fine with inhaler use and so on. But if you go to* ***a market like cholesterol, where you don't have any symptoms****, then for the doctors they're* ***much more GP driven needs****, so, to make sure that the patient doesn't get side effects, because if they're* ***not actually having any symptoms it can be very frustrating to try and maintain compliance****, but at the same time keep the workload down, so they hit the target cholesterol level, and they're not having the patient in and out. Because they have to manage workload. So there the* ***driver to prescribing and the needs of the doctor is much more about achieving target, getting to target quickly, getting to that efficiently, getting there without loads of side effects on the way, getting there in a cost efficient way*** *(G1.2).*

The choice of case studies characterised this diffusion influence well in that schizophrenia and erectile dysfunction are distinctly symptom-based, while patients with osteoporosis and hypercholesterolemia, at least in their initial stages, may be unaware of the existence of the condition. Based on the insights provided by respondents, in symptom-based conditions, the motivation behind clinical need from a patient's perspective appears to be related to their need to restore 'normality', taking into account social as opposed to just functional implications.

It's not the restoration of the erection per se which is the fundamental thing for a patient*. It's more around...just to give you why that's the case...Vacuum pumps were out, injections were out, you know, other things were around. If it was just about restoring the erection then, you know, why would Viagra, and Cialis be so successful?* ***Why would men*** *want to* ***take an oral tablet*** *that you take* ***an hour before, then wait, then have sex instead of just taking an injection and it's done****.* ***It's not the erection itself, it's what it allows you to carry on doing****. What this did, it not only solved that basic requirement of giving an erection back but also being able to* ***give men more freedom of the time that they're able to have sex, spontaneity, bring their love life back****. So patients got this (CS3.2).*

If you ***ask physicians what they think of tadalafil*** *(Cialis), they'll say that's the one that lasts a long time. That's the* ***one that lasts for 36 hours. And then they'll stop****. What they won't tell you is so that allows them to x, y and z and it means that this is what happens et cetera. And so when we did the research with physicians we felt well the uptake will be x amount. But what you found was that you then* ***went to the patients*** *and said to patients* ***'We'll give you a medication that lasts for 36 hours' and they got it instantly****. They thought 'Hang on a second.* ***That means over this weekend I can be pretty much ED-free****. That means that I can take it well in advance and not have to think about it'. When you look at something like* ***ED, it's more of a personal thing to the man. Physicians are very focused on solving the problem and the problem is a loss of an erection****. Therefore I can solve that problem. I sort it; my job is done. But the* ***patient feels the wider impact of that*** *and their partner does. So I think there's a* ***disconnect between the physician, what they believed that they were treating*** *and what their role was,* ***versus what the patient really saw as a true benefit*** *(CS3.2).*

Even in the absence of symptoms, a patient's consciousness of their condition and its potential implications seems to dictate the priority of their involvement in driving

clinical need. Based on some of the case study examples, it seems to be dependent on how much their life is impacted upon not only by the condition, but also the effects of therapy, as to whether patient need is the predominant driver for change. Respondents in the BP case felt that patients were influential in driving need for a treatment for osteoporosis that had long been trivialised as a condition of ageing.

> *I **think people's expectations have dramatically changed**. You now probably have well over a third of your life to live after menopause, whereas life expectancy being different in those days you probably didn't have a huge expectation of what your life would be after menopause, so I think people were really thinking if **they hit menopause at 45** and the average woman now **can live comfortably into her 80s**, you know **35 years of your life, how you live them and what your physical ability to cope in that area is going to be very much a driver in what shapes you interests** (CS1.1).*
>
> *I mean a patient who really is conscious of this will…**seek treatment from the menopause** all the way through and they can maintain good, bone health **for a much much longer period of time** than their parents would have done. And they **can live a much more active life** as a result, and that's got to be good (CS1.3).*

Patient dissatisfaction with complex administration protocols for BPs then became the driver for a formulation that was more convenient.

> *But then things changed dramatically here, and that was **the introduction of 70 milligram once a week**. And the once a week overcame this barrier. Because once a week, **easy, I only have to fast, swill it down once a week, wasn't a huge…wasn't 7 times the size of a tablet**, it was actually a small tablet, very nice packaging which was very patient-friendly, and that overcame the cyclical nature, **once a week, very easy to use, patient convenient, supported by this terrific suite of evidence, that changed everybody's behaviour**. The nature of the drug facilitates this because it has a very, very long half life, so the drug stays around in the system for a long, long time, so you could quite easily move to this type of a presentation of the drug, and off it went (CS1.3).*
>
> *Fosamax (alendronate) really took off when it did, and it really just comes down to the **biggest issue** in that was actually the **patient's desire not to go through a complicated administration** review. Didronel (etidronate) you still had to take it in a certain way. And that's quite inconvenient, **particularly for the type of patient we're talking** about (CS1.1).*

While schizophrenia is a symptomatic disorder, the affected individual may not be aware of the symptoms during certain phases of the illness and so in these circumstances respondents considered the needs of clinicians are likely to prevail in determining treatment choice. But in terms of staying on long-term therapy, respondents from this case study felt the patient-driven need was for an innovation

with fewer debilitating side effects compared with those of existing treatments that compromised any sense of restoring normal life for the patient.

In the statin case, Industry views suggested that need was strongly driven by clinicians and their necessity to achieve cholesterol targets set down by government policy in the incentivised Quality and Outcome Framework (QOF) (see Theme 4: Health service/policy environments; subtheme 4.1.1.1: Favourable policy environment). Respondents believed the asymptomatic nature of hypercholesterolaemia presented a challenge for clinicians as their need was related to ensuring eligible patients presented for treatment and maintained compliance with therapy in order to meet their targets, which is problematic in asymptomatic disease.

There's a relationship between the NSF and QOF and ***once you've got cholesterol indicators in the QOF and you've got indicators around creating disease registers****, and* ***patients having to have cholesterol readings, then that's going to drive use*** *(CS4.3).*

An analysis of Industry views suggests different degrees of clinical need can exist for patients with the same condition. While ED is not a life-threatening condition, for some patients their need was thought to be so profound, they were prepared to try any therapy irrespective of how unpleasant it was. This is often a mentality commensurate with treatment decisions in life-threatening conditions. However, at the other end of the spectrum, respondents believed there were patients whose needs were constrained by social stigma, which was an indication to respondents that a shift in cultural perceptions was required or a more acceptable mode of administration made available before patients would be prepared to come forward for treatment.

*If you think that **everything that had been used for impotence** or erectile dysfunction for years and years and years had either been **injections or bizarre and unpleasant remedies** that didn't work you know, and yet people who'd been trying to find a cure for this you know, for literally hundreds and thousands of years, it's just, it was one of the great ironies that we knew that we were going to go into discussions with the Department of Health about whether this should be reimbursed or what sort of restrictions be placed on it, but also simultaneously knew that this was **something that people had been desperately seeking to find a cure for because it had such a distressing effect on people** (CS3.1).*

1.5. Need to Satisfy Innovator Pursuit

Respondents suggested that clinical need can also arise from the innate personal characteristics of innovators; the need to be the first to experience new technologies and witness their effects in patients. Analysis of a limited number of views on this issue, leads to the notion that while not technically the scientific innovators of the drug, early adopters effectively become 'clinical innovators' through involvement in clinical trials. Respondents felt that this sets them aside from their peers by giving them knowledge insight that elevates them to the status of opinion leaders in their field (See Theme 8: Key opinion leaders; subtheme 8.2: Hierarchical cascade of influence/peer credibility). The danger of such innovator pursuit for novelty is that it may generate a need where there may not otherwise be a clinical justification for a new technology to be adopted.

*I think really the **key innovators** who are really running the basic science involved in the big clinical trials as lead investigators, they **want the next thing, they want to know something new, something that's not been tried** with the products, something that's a new indication, a new area, a new formulation, a new piece in the lifecycle management (CS1.1).*

*Opinion leaders, the **innovators**, also **want to be the first to try things**, even though they probably don't use it extensively, just because the **nature of their work keeps them away from patients** quite a lot (CS1.1).*

1.6. Industry Response to Unmet Clinical Need

Some critics of the Industry assert that they 'create' clinical need through the medicalisation of ordinary life. Respondents consistently presented the view however that they believed the origin of clinical need has to come from elsewhere (i.e. clinicians or patients) for it to be a genuine driver of diffusion. Unlike some clinical settings such as the medical device industry where surgeons may be involved in co-developing new technologies, the pharmaceutical industry relies on its relationships with influential clinicians (see Theme 8: Key opinion leaders; subtheme 8.1: Early engagement/collaboration) and utilises market research with clinicians and patients (see Theme 7: Market development; subtheme 7.1: Market research) as a means of identifying and understanding the issues pertaining to clinical need so as to know how best to meet them.

Interview data indicated that innovations can be:

- designed specifically to address the needs of a clinical problem – with the AAs, a new molecule was created to minimise side effects without impacting on efficacy;

- applied to a new clinical problem to answer a need, but where that specific clinical need was not the driver of development – PDE5 inhibitors were originally developed to treat hypertension, but the identification of a serendipitous side effect presented an opportunity for an oral candidate for ED;

- tailored/redesigned to answer a clinical need – with the BPs, a reformulation resulted in a reduction in the frequency of a complex dosing regime, which

presented an acceptable administration protocol for patients and improved compliance.

One respondent discussed how their attempt to influence what clinical need meant in the case of the AAs by redefining interpretations of efficacy from that of immediate alleviation of acute symptoms to one encompassing long-term outcomes (for the purpose of differentiation), was unsuccessful, as need in their view is defined ultimately by the adopter and not the diffuser.

> ***It's not just meaning you get a patient better now**, but you **should think about the long-term as well**, because if you think about some of **our competitors, they have issues with some fairly bad side effects that could get worse over time**, so it was about kind of trying to change a doctor's perception of what was important (CS2.3).*
>
> *The other thing we learnt there was if you go into a doctor and try and, at the time though we **tried to kind of redefine what efficacy meant to a doctor**, but efficacy to a psychiatrist **shouldn't mean that patient immediately gets better, it's that patient immediately gets better and then stays well**. It would sound a very reasonable thing to try and focus people that, when you make a prescribing decision think about now and the long-term, but actually I think in this market that doesn't really work, because **doctors might have that discussion with you and agree**, but then the next time they are **faced with somebody that's acutely unwell**, it probably **isn't front of mind**. **Psychiatrists don't think like that, they think here and now** (CS2.3).*

Some respondents highlighted how the extent of clinical need could be viewed as a potential barrier to the adoption of a new drug due to the financial implications that could arise from its introduction. While there was a need for BPs, respondents made the point that the prospect of treating all eligible patients would have been overwhelming and counterproductive to support their introduction by the NHS. Instead they targeted a tangible subgroup with manageable numbers to maintain a level of engagement with clinicians. The PDE5 inhibitor case demonstrated how the prospect of the sheer numbers of eligible men was considered to result in counterproductive restrictive government policy that severely compromised the anticipated diffusion potential of the drug.

*From the **GPs perspective**, it's **not in their interest for them to have a floodgate of people coming through the doors,** and if that happened all at once, it would probably be **counterproductive,** because it would be **unmanageable** and more likely to have negative impact on the product, if **they thought you were the instigator of driving that** (G1.1).*

*It's understanding how you can translate those features into benefits which relate and press the buttons for those customers which are relevant to their disease area. In this case it was actually trying to **narrow it down to those who had already had a fracture**, so there was already clear clinical evidence that someone had had an incidence of the disease and I think the **number of people having a fracture was more like I think 300,000, as opposed to 3,4, 10 million**, and therefore actually communicating and **discussing where this drug might fit in with a much smaller patient audience, and then one or two patients per GP a month was a much more palatable proposition** than it would have been to say 'there's 10 million people out there with potential kyphosis that is developing into osteoporosis'. The danger of doing that in your communications is that you will just switch doctors off. Because it's too big a problem to even think about, it's just too overwhelming (G1.2).*

2. CLINICIAN/PATIENT EXPERIENCE (EFFECTIVENESS)

In contrast to clinical need (Theme 1) which describes an ideal solution for a clinical problem, experience is the reality that is forged from using what is available in a real world clinical setting.

In the context of the case studies, respondents indicated four distinct aspects to experience that they considered were impactful on the diffusion of the case study drugs discussed:

- the need for clinicians to witness the effect of the drug for themselves, a subjective tangible evaluation based on personal experience;
- linking an improved experience to an innovation that makes the interaction with the patient easier (usually through more acceptable modes of administration);
- the lasting negative effect if a clinician's experience is distorted through inappropriate use of a drug, which could, in some cases result in safety warnings;
- the importance of clinicians gaining an insight into the patient's experience.

2.1. Subjective Evaluation Based on Personal Experience

Respondents indicated that clinicians perceive they have individual requirements that experience has to bear out before they accept the claims made to support a change to their behaviour. In this context, their perception was that evidence plays an important role in the early stages of diffusion by way of convincing clinicians to initiate

prescriptions, but once a drug is in use, the impact of evidence reduces and experience prevails in decision making.

*What **evidence will do is convince somebody to give something a go**. But at the end of the day there's **no substitute for good old fashioned personal clinical experience.** By the time it gets to **guidelines** people have **formed an opinion through their own clinical experience** anyway (CS2.2).*

Respondents expressed the view that when professional experience does not align with messages conveyed in clinical trials (even good quality studies), personal experience takes precedence. Once personal experience (or that of a respected colleague) confirms the benefits of a technology, adoption rates can accelerate through confidence to use the drug in patients previously excluded.

***What's really important is customers' personal experience**. If they have **used the drug and it hasn't worked, they are probably not going to use it again**, unless their colleagues say well actually I have used it and it worked, so I think they are perhaps more **driven by their experience and the experience of their colleagues** (CS2.3).*

***You got real market expansion because the doctors gained confidence**. They said 'now I can see **the patients, I always thought they would never be able to take these drugs', but this one they can give it to them**, so they had confidence in doing that. And that drove a complete change in attitude to the use of this class of drugs (CS1.3).*

*At this stage here in the beginning you're just...almost getting yourself a ticket to entry. It's a case of 'here's our unique point, this is why you should take any notice. And then you've also got a phase which says actually, you know, we're second and better though, you know. Look at the advantages that this is going to bring. **Look to your own patients. Look from your own experience.** And I think certainly at that stage...and that's **about three years in**, that people start saying actually, what would I prefer to do? I **have enough experience now to be able to make a decision on how these work** (CS3.2).*

Even those clinicians who may have been involved with the development of the drug from an early stage were believed to want to witness what is the real life impact these drugs have on patients outside a clinical trial setting.

*They [KOLs] are also interested in **seeing how the drugs perform in real life** after they've seen the trial results, they like to see it in real life to see if it actually does manifest itself (CS1.3).*

Even when later stage, head to head trials become available, the assertion was that a clinician's own experience continues to take preference – positively or negatively for an individual drug.

The head to head study against risperidone was published, I think something like a year after the initial launch. And I think, by that time, ***people's own personal experience had really helped to form their opinions****. And the* ***publication*** *of the Tran Study merely, I think,* ***reinforced in a clinical paper what people had already seen for themselves clinically*** *(CS2.2).*

Respondents suggested that views established in this way by clinicians remain deep rooted and can potentially lead to conflict with others, such as payers, whose decisions are more likely to be governed by published evidence. This was exemplified by the AAs where psychiatrists were thought to have brought their own reality to the data irrespective of what the evidence from clinical trials demonstrated, even if that reality was informed through erroneous use of the product at a suboptimal dose, as was the case with quetiapine (Seroquel).

There's been two big government studies recently, CATIE and CUTLASS, one in the States and one here, that actually is questioning the value of atypicals, that some people, particularly payers I think - are taking notice of. ***Psychiatrists I think are more sceptical of the data because they've had the clinical experience and they see a difference.*** *I think most psychiatrists, you know, would say no, I think atypicals are better. Payers are perhaps taking more notice of the data, so it would be interesting to see longer term what happens (CS2.1).*

Regardless of what your clinical data says, doctors don't perceive Seroquel to be as effective as either olanzapine or risperidone *(CS2.3).*

You then get things like experience use of product, and that would be at a wider population level and at a personal level because ***people always end up taking their personal experience significantly into account even if n=1*** *or invariably the patient got better, or the patient didn't, and that* ***tends to affect their prescribing quite significantly*** *thereafter (G1.1).*

An interesting insight into the wider issue of experience provided by one of the respondents related to how certain innovations can give rise to idiosyncratic responses in patients. In this case, there is thought to be a greater chance patients will be switched between medications and clinician experience becomes even more important. In mental health, psychiatrists were viewed as being more likely to try out

lots of different drugs or combinations to achieve the symptom control they need, compared with statins for instance, where clinicians can be reasonably confident that nearly all patients will respond to a particular statin in a certain way. The impact on diffusion was considered to be subtle, but over time could prevent a drug reaching its full diffusion potential. If this is indeed the case, it does provide an opportunity for late entrants to a class to gain some degree of market share.

> ***Nobody really knows how psychiatric drugs work…*** *it's* ***all theory****, and you still do* ***get an idiosyncratic response from patients*** *so they'll do well on, you know, somebody will do well on Risperdal (risperidone) and bad on olanzapine, and we don't know why, so* ***psychiatrists do like to try lots of different drugs and they use combinations of drugs to try and get the symptom control that they need*** *(CS2.1).*

Respondents described that offering drug samples is a way companies enable clinicians to gain experience without incurring a cost to themselves, or the patient. Sampling was particularly relevant in the PDE5 inhibitor case, not due to the unpredictability of response, but as a means of giving patients the opportunity to gain experience with the drug before deciding whether to bypass NHS prescribing restrictions and pay for a private prescription.

> *All three* ***companies sample their products****, so my impression from talking to doctors is they kind of softened the subject by saying look, I do have a* ***free sample that you can try of the product*** *that I am going to prescribe for you, therefore if* ***you take that product and it works, you can come back and get some more*** *on private prescription (CS3.3).*

2.2. Clinician-Patient Interaction

There was a consensus view from Industry respondents that changes to formulation e.g. from injection to oral, or from titration and routine monitoring to single doses, that make innovations easier to use can have a favourable impact on both the clinician's and patient's experience. The inference looking at the examples discussed

collectively was that ease of use ultimately translates to an improved social interaction between the patient and clinician.

What Viagra did was significantly change the market for impotence, you know, ***before all they could have done is prescribe an injectable*** *and now you know, when Viagra came to the market,* ***they had an oral treatment that made their life a lot easier****, so I think there's an emotional tie to it as well because it kind of* ***saved the day for them and so they feel very positive towards it*** *(CS3.3).*

It's probably the ***first atypical that you could use routinely****, yeah, I mean you* ***didn't need to do any monitoring*** *for it for example, there aren't any particularly nasty side effects, I mean it* ***has some side effects but it's not like clozapine where you, you know, you have to monitor patients for the side effect*** *(CS2.1).*

The thing that ***prescribers loved about Lipitor (atorvastatin)*** *was that it was, at its starting dose, because these drugs have a starting dose and then you can titrate up according to the kind of cholesterol lowering level,* ***at its starting dose, it was as effective as the highest licensed dose of simvastatin****, so it was a bit of a sort of****, fire and forget mentality*** *that people had. I don't want to make that sound, irresponsible and it was a* ***very convenient way of treating cholesterol*** *and that remained really the kind of unique selling point if you like for most general practice prescribers for a long time, certainly , through to sort of '03, '04 (CS4.1).*

Experiential associations with other drugs were believed to be influential in generating irrational long-lasting perceptions that can potentially affect the diffusion of new drugs. Respondents highlighted instances where clinicians' prior experience with certain formulations can pose a barrier to adoption of new drugs that utilise the same mode of delivery, even if used in a totally different context.

Psychiatrists actually have concerns about the prescribing of an injection*. It really stems back to the very first,* ***very old, treatments*** *on the marketplace were* ***mainly depots,*** *but they had quite* ***nasty side effects****. The oral atypicals were launched with Risperdal (risperidone) and olanzapine and the others, and* ***people really moved away from*** *that* ***depot medication and moved to the oral medication****. So they* ***hold quite negative views about injections in general,*** *so* ***even though Risperdal Consta is a long-acting atypical injection****,* ***they still have concerns about giving the injections to patients****, and they also I think, what adds to it, is that* ***if a patient is very unwell*** *and is admitted into hospital and is very florid in their symptoms, what* ***they sometimes have to do is they have to forcibly inject the patient just to calm them down*** *with a short-acting antipsychotic. And that, you know, I think also* ***gives injections a bit of a negative perception*** *(CS2.1).*

2.3. Inappropriate Drug Use

A predominant theme highlighted by nearly all respondents, involved the detrimental impact of inappropriate drug use on diffusion. If a drug is not used as intended, this

can alter the clinician or patient experience to such an extent that it can be very difficult for a drug to ever demonstrate its anticipated potential. The case studies highlighted how inappropriate use was believed to result in scenarios that ranged from distorted experiences of efficacy, to the more serious outcomes leading to the issue of formal safety warnings.

2.3.1. Distorted experience

Respondents indicated that confusion arising from unclear messaging, or insufficient differentiation of a drug from its competitors can lead to the clinician's experience becoming distorted and consignment of the drug to an unintended position in the treatment pathway.

For the AA class, improved efficacy was not the main driver of innovation. Respondents' understanding of clinical need was for a treatment with reduced side effects. Quetiapine produced fewer side effects at a dose that achieved equivalent efficacy to its competitors. However, the correct starting dose was not effectively communicated, partly due to various regimes being used in clinical trials. The resulting confusion led to quetiapine being used at too low a dose to achieve separation from its competitors on efficacy. Clinicians observed reduced side effects, but also witnessed inferior efficacy, and so the relative advantage was not experienced. This perception according to respondents proved difficult to rectify.

*The **doctor has been told the Seroquel (quetiapine) works**, but we know they are **not so much clinical evidence-based but own experience**. **They use Seroquel, they use it at too lower dose**, **it doesn't work as well as olanzapine, it doesn't work as well as Risperdal (risperidone), so they then have kind of negative perceptions**, so yeah, it doesn't have very many side effects, so they really buy into that, but **end up reserving it in a kind of second or third line position** (CS2.3).*

In the PDE inhibitor case, respondents felt that failure to position vardenafil correctly in the treatment pathway resulted in the agent being reserved for refractory cases when it was intended as a first-line competitor.

*I think if you look at **Levitra's (vardenafil) usage**, it's predominantly after; it's a very determined patient of which in this market there aren't many, who has tried Viagra (sildenafil), failed, tried Cialis (tadalafil), failed and thought well I'll give this a go because it's that or the injectables, I know what I'd prefer, so **we're getting the patients that have failed on the other two treatments.** This **wasn't our intention, because the chances are that they'll fail on ours**, so then the doctor's experience**, first experience with our treatment is that it's a treatment that doesn't work**, rather than **it's a treatment that does work because you've got a fresh naive patient** who's not tried anything before.(CS3.3)*

2.3.2. Safety warnings/concerns

Unlike clinical evidence where claims are based on statistical assertions of truth (discussed further in Theme 3), safety warnings may be issued on the basis of a much smaller number of events depending on the severity of the issue that has come to light through use in the general population. Safety warnings concerning their drugs were considered by respondents as the most detrimental as they can have a profound impact on diffusion and can leave drugs permanently tainted in the minds of some clinicians.

***To have two [Dear Doctor letters] was unprecedented to be honest with you, and to recover from two has been a massive success. You've got to add in competitors and how they use it** and so obviously **they'll use it negatively against you and positively against them**. So you have to really get your positive message out into the market one way or another. Whether that's through sales force or it's through meetings, through a combination of both really (CS4.2).*

*It's **difficult to recover from a safety warning**. There will be some physicians who would never, never touch it again with a barge pole. There will be **others who will want to see longer term data**, and there'll be **others that will base their judgment on their own clinical practice and what they've observed** (CS4.3).*

*But when you have an **issue of adverse tolerability** like this which is causing oesophageal irritation. **They're caustic drugs, they're designed in a way, it's a nasty acid but it diffuses once it gets in the gut,** but you know, with an elderly population you often get reflux and that can push the acid back into the oesophagus. And the competition made hay with that. And consequently **we got a relatively slow uptake curve,** even though we were **promoting quite extensively doing a lot of education and advertising, calling on doctors, we couldn't change behaviour because this was the message that they'd got in their head from the competition**, and, to be fair, patients were referring…you know, **we did have instances where patients were actually reporting this to the doctor** (CS1.3).*

Industry views suggest a spectrum of impact of safety issues. Those with most significance were considered to be the mandatory warning letters issued by authoritative bodies such as the Committee for the Safety of Medicines (CSM)[16] that have national coverage.

> *Probably the biggest impact on Risperdal (risperidone) negatively was this -* ***the CVAE[17] warning from the MHRA, that, you know, Risperdal shouldn't really be used in elderly patients, that had quite an immediate impact upon sales****…I've* ***not seen anything like it before or since*** *then I don't think, but in terms of like* ***the letter went out from the CSM, and it was literally patients were switched****, which, you know, is unusual but it* ***happened very fast*** *(CS2.1).*

For the particular case studies concerned, the safety warnings were not due to the products *per se*, but resulted from incorrect or unapproved use of the products by clinicians and patients (AAs: off-label indications; BPs: non-adherence to administration protocols; Statins: use at too high a starting dose). Nonetheless, respondents indicated the need for a robust response to limit the damage to the drugs' continued diffusion.

> ***When rosuvastatin was first being used, it perhaps wasn't being used appropriately by clinicians****. They'd been used* ***to using simvastatin and atorvastatin for however many years at kind of reasonably high doses****, 20s and 40s, and they* ***were using rosuvastatin in the same way despite the starting dose being 10mg****. And they were actually four* ***cases of rhabdomyolysis associated with starting patients on higher doses of rosuva*** *than there should have been which* ***prompted a letter from the regulatory authorities*** *to remind prescribers that the starting dose was 10mg. And so* ***once you send a letter from regulators and with what looks to be a safety concern then that's going to have an impact*** *(CS4.3).*

Off-label (off-licence) use of drugs is a discretional practice that is more likely to be associated with safety risks as the drug has not undergone licensing trials for that indication. While respondents indicated it is not a practice Industry can endorse, they

[16] The Committee for the Safety of Medicines became part of the newly established Commission on Human Medicines in October 2005.
[17] Cerebrovascular adverse event.

suggested it can enable clinicians to gain experience with a drug. In the case of BPs off-label prescribing was not regarded as a strong driver of diffusion.

> *I mean if **people have used it in a certain area and found it works very well**, then, you know, **once it's licensed they would be inclined to use more of it** (CS2.1).*
>
> *We were very clear and ethical about this, **that if you'd got somebody on HRT who is osteoporotic you've been treating with HRT to treat osteoporosis, then, yes use alendronate, that's a very good alternative** for you. But **if you've got somebody on HRT and they're 50 and they're doing this for menopause management it is not appropriate to use alendronate at that stage**. **Some doctors would out of their own choice, but it's not what we were saying**. And you will see on that chart of adoption of HRT when it does come down there is **some change to our growth curve but it's not that dramatic, it's not the driver** (CS1.3).*

Off-label use however, attributed to a significant increase in usage of AAs but the subsequent safety issue that practice incurred was responsible for a tangible decline in their diffusion.

> ***Risperdal (risperidone) was increasingly being used in elderly patients with psychosis**, some of the prescribing was **off-licence**, you know, that the clinicians had just decided to use that, but **once Melleril (thioridazine) was advised not to be used** by the Committee for the Safety of Medicines, a lot of **patients were actually switched over to Risperdal**. What then happened here was that there were some **studies done with Risperdal and some of the other atypical antipsychotics, which actually suggested that Risperdal probably had some risks as well in elderly patients**, it was an independent study. And then what happened was that patients - some of the elderly psychosis patients **were switched off Risperdal onto other drugs, so we gained there and then began to lose business here** (CS2.1).*
>
> *I tell you what happened here, it was **safety concerns, we had dear doctor letters, and so did Risperdal. Issues with dementia** (CS2.2).*

Analysis of respondents' views highlighted how the sensitivity of both regulators and prescribers to safety concerns can be influenced by previous and concurrent incidents, not necessarily limited to the particular class in question. Respondents discussed how withdrawal of cerevastatin resulted in an atmosphere of caution amongst regulators, such that the tolerance for issuing a safety warning was much lower for newer statins, when the issue was perceived by respondents as being due to inappropriate use rather than an innate characteristic of the drug.

I think that ***the regulators were also a bit more cautious and were keen to issue a letter because of what had happened with cerivastatin****. Because it was rhabdomyolysis which, they had fatal cases of rhabdomyolysis; I think there were 50 odd cases of fatal rhabdomyolysis so the regulators are now in a more cautious place and keen to act quickly. So* ***once you kind of send a letter, a prescribing reminder that's citing a risk of rhabdomyolysis in a market where there's already been a product withdrawal because of rhabdomyolysis then that spooks physicians and that's responsible for some of that uptake****. This is* ***also kind of the time frame when there was a real gearing up behind simvastatin*** *as well. So* ***put those two things together and that's the kind of flattening off, the less steep trajectory of that line*** *around kind of late 2004 onwards (CS4.3).*

And at the same time, kind of 2004, you had the withdrawal of Vioxx and various other kinds of scares, so ***for rosuvastatin being a new entrant into a market where there'd already been scares that definitely has an impact on diffusion*** *(CS4.3).*

While a safety warning may be produced to call attention to and rectify issues of adopter misuse, from an Industry perspective, the release of a formal safety warning is detrimental because it highlights a potential problem with the drug in the minds of prescribers and patients. The impact may extend beyond that of the affected drug to impinge on the whole class, which can give rise to polarised responses from competitors. Respondents indicated how the bearing of regulatory concerns can be lessened if competitors respond altruistically with a view that it could be potentially damaging to the perception of the whole class. Alternatively if the problem is perceived by competitors as drug-specific, then the warning may be utilised to distance that drug from the rest of the class.

Bisphosphonates are not a very nice class of drugs to take*.* ***Didronel (etidronate) was a cyclical bisphosphonate*** *so you took the active ingredient for a certain period of time, and then you took calcium for a certain period of time. It was* ***not a very easy thing to take but people were used to doing it****.* ***Our once daily came in, we had a fracture intervention trial which came through in publication '96, the FIT trial, so that gave you the evidence base, it was very quick after launch, and every expectation would have been then that this drug would have flown****. There's a big population which is under treated, existing therapy not particularly attractive for anybody to take, patient, doctor. But,* ***at the same time*** *as we had this,* ***we did have an incidence of adverse tolerability particularly in the United States which led to a world-wide need for us to write a 'dear doctor' letter****. You know, an awareness letter to the doctor saying '****watch out for tolerability****'. Well then you see* ***your competition, some will walk away from that, and say 'that's going to be really bad news for growing this market' and some will say 'that's great news, I'll keep my market share',*** *so it depends on whether the motivation of the competitor is market share or market expansion (CS1.3).*

At the other end of the safety spectrum is the gradual change in attitude towards a drug based on experience of safety concerns that arise only after long-term use. For the AAs, the initial perception that their side effect profiles were more acceptable has become the subject of scrutiny during the later stages of their lifecycle.

In the last probably eighteen months ***people do have real concerns about the metabolic effects. It is causing people to switch away from olanzapine gradually in schizophrenia, but they've not moved away rapidly because again I think the efficacy is still seen as the most important thing****, and the company have done quite a good job in trying to* ***minimise how the side effects are viewed*** *(CS2.2).*

Other case studies however, provided a contrasting view on the impact of safety issues. One respondent highlighted how safety concerns can be utilised in a positive capacity by Industry as a means of demonstrating how thoroughly the drug has been tested, which from their perspective adds to the credibility of their messages.

I think it was ***very helpful that it had a nitrate contraindication in some respects, because I think people knew that we'd checked****. I mean obviously we are always going to check what the side effect profile is, but you know, as somebody put it to me; somebody pointing out where the iceberg was, meant that you knew how to sail the ship. So think that was very important (CS3.1).*

2.4. Patient Insight

As well as witnessing the effects of the drugs in patients, respondents suggested that the experience of clinicians is augmented by patient experience. This has a greater impact for those drugs that produce tangible benefits (such as PDE5 inhibitors), but for other drugs particularly for osteoporosis, it may take several years before efficacy is realised and therefore patient insight in this capacity relates more to issues of tolerability.

This is a market place which is extremely receptive to both noise and people talking to you about it, because ***for a physician it's something they can do something about,*** *as well. It's* ***not a long drawn out treatment*** *and a difficult area to treat and pretty much the patient will tell you, if you ever get feedback, but* ***the patient will tell you has it worked or hasn't it****. And the patient is able to define that.* ***It's not a case of...to take osteoporosis*** *that you mentioned earlier, you know. If you've got a* ***lady with a couple of vertebral fractures, how do you know if your bisphosphonates have actually been efficacious, because you've got to wait ten years.*** *And if she has a hip fracture at eight years, does that mean that she was...that it didn't work? Or does it mean that she would have got it at two years? (CS3/ INT2).*

A clinician's experience impacts on prescriptions, but a patient's experience indirectly impacts on diffusion through compliance. As with clinical need (Theme 1), patient experience is heavily influenced by the course of the disease and symptom severity. In the case of the AAs for example, respondents indicated for some patients with schizophrenia the fear of experiencing a relapse of their symptoms may be of such magnitude that it is sufficient to offset issues related to the adverse side effects of the drug. If patients also experience a sense of benefit from the medication, they also have a greater incentive to continue taking it. Conversely, in conditions such as osteoporosis and hypercholesterolaemia, a lack of apparent initial symptoms and therefore no obvious medication benefit, can potentially lead to complacency, which respondents viewed as a major barrier to compliance. Respondents considered that where patients feel some control over their medication, compliance may improve, which ultimately via feedback to prescribers, can have a positive impact on diffusion.

I think, you've got to be able to have that conversation with them [the patient] around, you have a ***side effect and you have to offset that with the benefit*** *of what you're getting from it. And this is a patient that you don't want to de-stabilise if you've managed to get them well, that's why you have to manage side effects and all products have side effects. That's a dialogue between the prescriber and the patient but we need to help with that dialogue, so we* ***put a lot of stall around helping the prescriber have that dialogue with the patient, which is yeah you'll get side effects from the medication so let's talk about what they are, let's talk about….it's risk versus benefit, don't ever forget what you're giving up around keeping you well.*** *You'll probably never see one of these patients in relapse but what they go through is pretty horrific and* ***no patient ever wants to go back in****,* ***one thing they fear most is relapse*** *(CS2.2).*

We also know through market research databases that are available to us how long people stay on therapy. *And so we know there is a* ***big decay curve for nearly all chronic therapies****, and that's a big problem for, well, it's been* ***opportunity lost to the industry****,* ***but it's been cost for the health system*** *because people who don't adhere are going to cost you money at the end of the day (CS1.3).*

***With lipids** a lot of patients don't, they realise they've got it but **they've got no real side effects from it**, then you find the patients **take the high cholesterol a bit more seriously when they've had an MI or a stroke** or something else. Therefore the **motivation to take the tablets is a lot higher in Parkinson's, cancer, whatever, where you can physically see what the drug's doing to you in terms of curing your symptoms that you've physically got** (CS4.2).*

Respondents discussed the notion that a drug's 'worth' may be judged by a patient with greater scrutiny for asymptomatic compared with symptomatic conditions. In asymptomatic conditions, the disconnection between the physical act of taking the drug and experiencing an improved health state can reduce a patient's tolerance to inconvenience, such as adverse side effects or administration complexities. In the BP case, where symptoms of osteoporosis are not immediately obvious, the respondents believed that patients were not as willing to accept a new drug that impacted adversely on their daily life.

*The other thing with these drugs is that you do have **to take it with a large volume of water in a fasting state at the beginning of the day**. Well, for an **elderly population that is often very inconvenient**. You know, your 70 year old lady in this country, not necessarily the wealthiest part of the population, you know, they like to get up in the morning and have their cup of tea don't they? **So that was also a barrier** (CS1.3).*

Respondents indicated that they underestimated the impact of complicated dose regimes of BPs for the patient. Their belief was that by shifting from a cyclical dosing regimen to single daily dosing, this would overcome patient compliance issues, but due to the associated risk of oesophagitis with alendronate, the complexity issue re-emerged through complex administration protocols. In the PDE5 inhibitor case, respondents suggested low compliance resulted from patients perceptions that therapeutic effect was inconsistent with normal sexual activity i.e. intimacy and spontaneity were compromised due to the pharmacological constraints of the drug. This was further exacerbated by government prescribing restrictions.

It's little known that about ***two thirds of patients discontinue their therapy within three to six months****. The reason for that is generally because...you've got to almost put yourself in the* ***mindset of a man who's 40 plus with ED****. You know, you never really thought this was going to happen. Nobody ever talks to you about it. Then it does happen and, as a man, you don't talk about it. That's the last thing that you do. And* ***not only do you lose your erections, you also lose all the intimacy that you have with your partner****. You start withdrawing from some of the daily things that you would do. Not the act of sex itself, that's an absolute no-no. But what you stop doing is, you stop holding hands. You stop cuddling on the sofa. You stop the little bit of banter between you and your partner or your wife of 20 plus years because what happens if it leads to that thing which I can't do any more? And so it becomes a psychological barrier.* *You go and get treatment and you take your medication and for* ***Viagra*** *to work you need to* ***take it on an empty stomach, take it an hour before anticipated sexual activity and you've got four hours in which it works.*** *So ultimately as an efficacy restorer it will restore your erections. But what it* ***doesn't allow you to do is completely restore those other elements*** *because under* ***government regulations in the UK*** *you can...the recommendation is that* ***you get four treatments per month****, enough for one per week, which is pretty much interpreted as four per month. And if I have four in the cupboard I only have four opportunities lasting for four hours each time,* ***I'm going to plan****. And I'm going to ensure that I* ***do not waste that tablet****. So it's a case of '****Do I use them all in the first week and have a normal life as it was before*** *but then don't have any for three weeks?'* ***Or 'Do I ration them out****?' I'm going to ration them out because that's what men generally do, which means that you start to completely plan your sex life. So it will restore the erection back but it's not going to restore the other bits of intimacy (CS3.2).*

The consensus view from Industry was if clinicians and patients cannot be convinced on the basis of their experience that a drug offers relative advantage that meets their needs and expectations, whilst uptake may not initially be affected as that experience is being gained, the drug's overall diffusion may be reduced.

2.5. Industry Response to Experiential Barriers

Analysis of respondents' views suggested experiential barriers are particularly difficult to uncover and can be difficult to change. While adopter behaviour is beyond their control, respondents described a perceived sense of responsibility for inappropriate use, seeing it as a failure in their communication efforts. Communication strategies employed by respondents to encourage clinicians to re-evaluate their practice and view the drug in the desired way had varying degrees of success and increasing patient compliance was equally challenging, even once the root cause of their discontent was known.

We did a lot of work in terms of ***understanding what were the misconceptions****,* ***what needed to be communicated more clearly,*** *and also what materials we could provide that may support the customer. So* ***what could support the GP or the specialist to make it easier for them to work with the patient****, so if they had some uncertainty around what they needed to do, they would* ***have some support items that were purely educational*** *and they'd be able to sort of say, okay, if they gave the drug, or any drug, to the patient 'here's the leaflet to say this is what you should do and how you should take it' (G1.2).*

Regardless *of what your clinical* ***data*** *says,* ***doctors don't perceive Seroquel (quetiapine) to be as effective*** *as either olanzapine or risperidone****. Even when NICE guidance says it is****,* ***our doctors don't believe it, because their experience is it doesn't work as well.*** *So unless you get them to kind of* ***re-evaluate and use it at the right dose…their perception won't change*** *(CS2.3).*

One of the ***holy grails of the industry*** *is to find a way to* ***support doctors and patients to help the patients to keep taking medicines*** *because any drug that we do any kind of research on, we find that* ***there's an enormous drop off from the first prescription, very few people are still taking even chronic medicines 12 months*** *after they were first prescribed them, people just stop,* ***they don't like taking medicines****, which is not good for them and its certainly not good for the prescriber who's, made an investment of his time, his or her time and NHS funds to make the medicine available thinking that they are embarking on a chronic course of treatment and actually they weren't, but* ***despite every which way we've tried to sort of help with educational materials or reminder programmes or programmes put into pharmacy****,* ***I don't think anyone has really convincingly shown that any programme really has an impact on how long people continue taking medicines*** *(CS4.1).*

The unique characteristics of the pharmaceutical market were highlighted by respondents as an explanation why from their perspective it is critical to get communication accurate at launch.

Basically, we're completely unlike any other market, that if you look at all the data, you ***essentially get one bite at the cherry in pharma****, and* ***if you're not successful the first time around you never can be again****. I mean it's not like making a cereal or something, because if that doesn't work you can change the formulation. You can't* ***with a drug, you've got what you've got****, and the only things you can therefore affect are price, packaging to some extent, and that's quite limited, our promotion is actually quite restricted under the guidelines, the conduct and so on and so forth. So actually* ***if you don't make the best you can of that and try and get rapid uptake, you will never regain that*** *(G1.1).*

Where adoption was affected by miscommunication, the factor that made the difference to the continued diffusion of a drug appeared to be related to the manner in which the Industry reacted to the problem. Respondents indicated how development of services to manage the impact of side effect issues was employed to dissipate the reaction to mounting concern in the AA case. Respondents took the

view that a holistic approach to perceived problems can be successful in minimising any negative impact on an individual agent or class of drugs.

We talked about ***weight, diabetes and those being issues****, well it's not….****these patients have those anyway but then our customers are still having to manage those patients****, how can we help?* ***Weight gain is clearly a side effect of our drug so we need to develop a service****, you know, the* ***other side effects aren't*** *but could we just* ***stand back and say we're not going to do anything about it****? Well actually no because that's* ***not going to help our throughput of patients long-term and it's not going to help our customers understand the issue****. We've got* ***a service that we're now training NHS personnel on…how to manage physical health in schizophrenic patients*** *that's endorsed by all the advocacy groups, endorsed by the government and that's taken us a lot of time and a lot of money but we think that's really important and as we are the* ***market leader we should be leading the way on the other issues that need to be addressed*** *(CS2.2).*

An analysis of respondents' views, suggested that new drugs entering a class that has experienced safety issues are at risk of condemnation by association. Respondents indicated the importance of dissociating the new drug from any features or descriptions that could lead to a connection with the outlier. In these circumstances, tensions can exist between the need to emphasise the key points of difference to make it a desirable alternative, with the need to remain sufficiently synonymous with the class to prevent it from being more closely aligned with the outlier.

There was ***a lot of anticipation****, it was* ***called the superstatin and megastatin*** *and all kinds of…gigantastatin and all kinds of odd names before it came to launch which* ***helped and hindered*** *of course…****cerivastatin*** *had been withdrawn and that was dosed differently to other statins, it was* ***dosed in micrograms. So it seems a more potent statin and then you come with a megastatin****, I quote, and all of a sudden* ***people are trying to link that back****. The fact is that* ***cerivastatin was a completely different molecule really to the rest of the statin class****. Hence it's dosed in micrograms, it was very lypophylic, the side effects profile was slightly different to the rest of the statin class which are largely exactly the same.* ***It wasn't just us who had to move cerivastatin to the side, it was the whole class.*** *(CS4.2).*

I think ***cerivastatin came to the market claiming superior efficacy and gets withdrawn****. Effectively* ***rosuvastatin had to kind of try and do something similar, new statin to the market, proven superior efficacy in order to get usage****, definitely had an impact****. What you have to do is to show the safety data and say look here's the adverse event reporting data, you can see rosuvastatin is in line with the other statins and cerivastatin is on here as well and it's off the scale****. Other than that, it's actually quite difficult because it's quite an emotive response you're dealing with amongst physicians in terms of their level of comfort around prescribing something new (CS4.3).*

The response to safety warnings also needs to be managed sympathetically to reassure prescribers and abate any concerns that may be further fuelled by competitors.

It's just a ***case of reassurance, to present the safety data in context against the other statins****. To try and demonstrate to physicians that look, it's exactly in line with the other available statins. Perhaps* ***we did have a bit of a problem in terms of the way that the product was being used, that's now been addressed*** *and the initiation rates at the start dose are actually very good and actually much better than what you'd get from the SPCs of the other statins (CS4.3).*

When the dear doc letters came out in some ways there was a programme of meetings to sort of say, you know, don't worry about it. I often do wonder if the fact that you say to someone don't worry, they worry more*. Like don't worry about flying, the first thing you do is like it's going to crash. I think that maybe was a mistake to go so passionately across the country saying don't worry, it's alright. It* ***might have just been better just to say carry on almost as normal and say yeah, we do have side effects, but they're in line with the rest of those in the class*** *(CS4.2).*

3. CLINICAL EVIDENCE (EFFICACY)

Clinical evidence is the data derived from trials involving sufficient numbers of patients to demonstrate the statistical truth of an assertion. It differs from experiential evidence (Theme 2) in that it is the generation of data under controlled ideal conditions rather than real world clinical settings. It ranked highly with respondents when discussing influential factors on diffusion in generic terms, but in the context of the case studies, respondents did acknowledge that it sometimes played a peripheral role in decision making compared to some of the other themes.

3.1. 'Marketing' Evidence

An analysis of respondents views revealed that clinical evidence appears to serve two distinct functions from their perspective; the first is to fulfil regulatory requirements for licensing; the second is in a market access capacity to communicate information to clinicians and payers involved in decision making processes during the adoption phase, or as a means of potentially reviving interest in a drug during the later stages of diffusion.

*Clearly the **trial designs** that are **done for regulatory purposes need to also meet the needs of being able to communicate the benefits of the medicine to the wider community**, because you won't have typically in market studies for some years until after the medicine is launched. So you **need to have robust data which is going to be able to present to people, regulators, to payers, to physicians, to everybody that actually gives a compelling story of why we would use the drug**. So marketing gets involved before launch is what I'm saying (CS1.3).*

*I think possibly **one of the reasons why we stay down this end of the market is because we don't do as many studies or trials** as the other two products, and we all know; it's almost like a self-fulfilling thing, **we don't do as many because we're not making as much money, but you know we might make more money if we do more studies**, so I think it definitely; **from a marketing point of view, it really helps, because you can keep saying the same things but bring new data to the package which then makes it sound new and interesting**, whereas if you've got old data that you're just sort of re-hashing all the time, you struggle to make something sound new or interesting, so I think clinical data does have a significant effect (CS3.3).*

The use of evidence as a tool to promote the diffusion of a new drug inevitably links it to marketing. Some respondents believed that the usefulness of evidence, regardless of its quality, in aiding clinical decision making was directly related to a company's ability, and budget to communicate findings. Without this level of promotion, respondents indicated that the potential impact of good evidence could be lost, rather than consider the possibility that this information might be sought independently by prescribers. Others preferred to see evidence as a separate entity, regarding it to be an independent endorsement of marketing claims.

It's a very highly regulated industry in terms of what you can and what you can't present to clinicians. ***We can*** *convey* ***the results of clinical studies and you can say that that's marketing, you can say that that's science****. But I think there's a case to say that it's…certainly in the UK it's, it's pretty difficult to over market a drug just because of the level of regulation. It's that* ***relationship between regulation and marketing*** *and* ***some of the sign off procedures that we have to go through internally such that the representatives can actually share the material with a physician are kind of ludicrous*** *but it's there to protect the industry and the clinicians (CS4.3).*

The data possibly helped to drive some of it, but I think more of that increase you can see was actually driven by the use in elderly patients, I mean ***the Csernansky data was very very good data. You probably could have argued that we didn't do enough with it****, you know, in terms of promoting the data, because it's very good data. Just limits in terms of marketing spend, you know, Jansen-Cilag would generally have a much lower marketing budget than Lilly for example (CS2.1).*

We had good effective ***marketing*** *that was key* ***in driving the success of the brand****.* ***We had to have the clinical data as well, but the marketing activity I think really had more of an emphasis on driving the brand's success.*** *Now I think you can - you still have to invest in the marketing, but* ***unless you have the clinical data to back up the marketing, it's far less effective*** *(CS2.1).*

3.2. Impact of Clinical Evidence

Analysis of responses has indicated that there is a loose correlation between the type, volume and quality of evidence and its impact on clinical practice. Respondents discussed numerous examples where 'experiential evidence' has taken precedence over clinical trial evidence. In contrast, other examples such as the statin case have shown how evidence was central to transforming clinical practice.

The first large scale trial in the AAs merely served the function of confirming clinicians' experience. The need in that area for a new drug was so great, respondents felt evidence was almost peripheral to the decision to prescribe. For a later entrant to that class, while there was evidence to indicate a more favourable profile, it did little to elevate its market position, suggesting that other factors were influencing their decisions. Respondents discussed how evidence from one of the major trials in the BP case did not impact at the point of publication, but instead was only applied once other barriers to the use of the drug were removed. In the PDE5 inhibitor case, robust trials indicating alternative preferences to the market leader were perceived by respondents as doing little to alter prescribing behaviour, and in the statin case, the trial that did change behaviour was only able to do so by demonstrating tangible, as opposed to surrogate endpoints at a point in time when perceptions were already believed to be starting to move in that direction.

From the respondents' perspective, evidence does not seem to change behaviour by itself. Rather it is one of a number of factors that influence diffusion, the importance of which is often dependent on market entry position. For the first and early entrants, evidence appears to serve a role to change consensus approaches to practice, while for later entrants evidence becomes a tool to differentiate between drugs and so may be more likely perceived as marketing. Only in the case of safety concerns was independent evidence seen by respondents as crucial for its credibility to reinstate confidence in a 'tainted' drug.

*I think if **we hadn't had these Dear Doctor letters this gap here shows you the evidence is not that important**. **It is now because this happened and people want to see evidence**, so if you start it again here, you'd say yes some of the trials have been important but **during that first dynamic phase evidence wasn't important to us. Everyone had bought into the fact that lowering LDL is good for you** (CS4.2).*

Our objective is to become the number one oral atypical, and actually, ***if all these drugs work exactly the same****, you know, so* ***in terms of their level of effect is the same, and that's what NICE says****,* ***why is it that the drug that actually causes patients the least problem is only 3rd not 1st in the market****?... it should be a lot higher up than it is (CS2.3).*

Phase III trials were regarded by respondents as the most powerful in terms of influencing behaviour, but while a first entrant can reap the benefit of its position by using licensing trials against placebo as marketing tools, the suggestion was that the bar is raised for later entrants as quality becomes synonymous with the ability to show differentiation from class competitors through head to head studies. In doing so, it is replicating real world clinical settings that are of practical use in clinical decision making (see subtheme 3.2.2.1: Head to head comparisons).

Quality of the data is absolutely paramount to us for a successful product launch*. We have to* ***do placebo for regulatory reasons****.* ***Physicians want head to head, how do you compare with other products on the marketplace****? If you're lucky enough not to be, you know you're first in class then it's slightly different but quality data is critical (CS2.2).*

Trials get you your position in guidelines, and there are ***different qualities of trials*** *of course. You've got your phase III* ***regulatory filing, which is against placebo, which just shows the thing works****. If it's a* ***highly competitive field, people like to have head-to-head studies versus the leading comparators, or use drugs in the field at the right dose so that they can make a valid judgement call saying 'well this one is better than that one' and they can say they're efficaciously the same but one does this with less side effects and therefore is better pay off for the doctor and the patient.*** *And that will then influence the positioning in the guidelines, so you have to have the trials, the best form of course, which really prove outcomes (CS1.3).*

Efficacy, that has to be proven with all drugs, so you have to have clinical data that shows you're efficacious, and clinical data that shows that you're well tolerated as well, but efficacy is probably the one driver across all brands. ***The most powerful data is sort of, you know, the early clinical data, so the phase IIIb, particularly if you have randomised head to head, you know, double blinded type data****, I mean that's* ***regarded as the most powerful data****. The* ***systematic reviews are generally regarded as not quite as robust sometimes****, although they can be very useful in terms of gathering lots of different opinions together and forming and overall consensus (CS2.1).*

3.2.1. Trial design

Trial design was a factor highlighted by most respondents as being influential and yet its effect on diffusion can easily be overlooked. Respondents discussed examples of where one company's strategy can be undone by a competitor's trial, often fortuitously, if it allows the competitor to make claims in certain subgroups in advance of the company's own research reporting. Although fortuitous outcomes

may not be viewed with the same degree of confidence as prospectively planned outcomes, respondents indicated how they diminish the impact of subsequent trials specifically designed to report these outcomes.

I think what disappointed us, and I think there's two things, one is fortuitous, I think that the ***bisphosphonates are a very good class of drugs****, so I will be honest with you I think they all work, and they're* ***all substantially above what you're basic calcium vitamin D does****, so that's the great news for the class yes? The bad news, because they all work, that when you try and plan in 1993 what you're expecting breakthrough to do, which was that* ***we were planning to show a significant reduction in hip fracture that no one else would have, we actually got trumped by Fosamax (alendronate) because they showed fortuitously because it was never powered to show it, they showed fortuitously that they did significantly reduce hip fracture in their trials****, because they had a good drug, and we had a good drug, you know, so the reality is that* ***had they not shown hip fracture, had they only ever shown vertebral fracture, which is what we were predicting at the time, then ours, because it was powered to show hip fracture, should have been able to do the bit where it became the market leader*** *(CS1.2).*

3.2.1.1. Functional versatility of evidence

Several respondents highlighted issues in relation to how evidence has to serve multiple functions for different stakeholders, making trial design complex. They provided an insight into how in the first instance, trial design is heavily influenced by regulatory requirements. However failure, for example, to satisfy the regulator requirements in one country can have adverse knock on effects globally. Regulatory scepticism from an authoritative source was considered to inadvertently impact upon the initial uptake rate of a drug in other countries.

Regulators around the world all have different, slightly different nuances on what data they want to see*, which makes it expensive to bring a medicine to market, because you* ***can't necessarily use the same file around the world, and that is a frustration through the industry, and it slows access to medicine down****.* ***And it costs us money****. So that's a frustration, but that's the world that we live in (CS1.3).*

There is genuinely a concern that etidronate as a first generation bisphosphonate, that ***if you give it in too higher a dose then it causes osteomalacia which is basically malformed bone, so that the bone that it's making is not of a sufficient quality****. And we know that, it came out from the sciences, and the solution from a scientific point of view was to give it in cyclical regiment****, so that's why it became Didronel PMO (etidronate) and had a cyclical regimen*** *of 14 days of Didronel followed by the calcium, vitamin D…that's all done to stop osteomalacia occurring because in that dosing cycle it doesn't happen. The* ***US has higher concerns about that than the European regulators, so, it's not unusual that different regulators have different concerns****. You could, as a company,* ***submit new data to shift the opinion of the regulators****,* ***but you reach a point relatively quickly when you get regulatory delay****, that because of the intellectual property rights that you have on the product it*

becomes unviable to bring it to market within the time space you have back to actually recoup your additional costs *and your base costs. It* ***(etidronate) went on and got a licence in Europe, but it never managed to get a licence in the US*** *(CS1.1).*

An analysis of respondents' views showed how adaptation of clinical evidence to fulfil functions beyond licensing requirements is dependent on designing a trial programme from the outset that takes account of the needs of all stakeholders involved at different stages in the diffusion process. Such foresight to accommodate cost effectiveness outcomes within the clinical effectiveness studies was believed to pay dividends in terms of diffusion by reducing any potential delay in overcoming both the regulatory and payer hurdles to the market. The Fracture Intervention Trial for alendronate was designed to produce outcomes relevant to all those concerned in a timely manner soon after launch. Respondents highlighted how carefully planned trial programmes can also lead to approval of new indications many years ahead of competitors, as demonstrated in the AA case where olanzapine obtained a secondary indication in bipolar disorder four years ahead of risperidone, despite entering the market for schizophrenia three years after risperidone (see Theme 7: Market development; subtheme 7.4: Research - new formulations/indications).

For registration you have to have two placebo controlled studies for licence, so that's why people produce placebo, because we have to, the regulations to actually get the drug licensed. What the regulators want versus what the market access side want, are completely different things *(G1.1).*

In the alendronate case for us it was very important that we had the fracture intervention trial which was published in about 1996. For a big outcomes trial, three year outcomes trial on fracture which really ***no fracture data of that scale existed in this field before that trial****, and to bring that to market less than a year after the launch of the drug was a hugely important thing to do in getting the diffusion of the drug in a very under treated disease. So, that was a good example of a huge …of this* ***designing the trials correctly for phase III to be extended to produce the outcomes which gives you every argument*** *(CS1.3).*

One of our key things is ***who do we need to talk to****? Where is the funding?...****Who needs taking into account when you're generating your evidence*** *(G1.1).*

The concept of multifunctional trials can however be a costly and risky strategy for Industry, particularly as the impact of evidence on diffusion, as demonstrated by some of the case studies, is variable and not necessarily the panacea in clinical decision making that wider general consensus generally alludes to.

3.2.1.2. Novel trial perspective

Analysis of Industry insights suggests that having a unique angle in trial design can increase its impact. The case studies have often shown that despite a plethora of primary evidence, only those pivotal trials that offered a unique angle such as unprecedented trial size or length of study, were recalled by respondents as being used to promote the product. The minimum trial size is set by the primary outcome being investigated in order to statistically show a difference in effect, but large numbers of participants may be recruited as a means of lending greater credence to the trial. Prior to the Tollefson *et al.* study (1997) that included nearly 2,000 patients, AA trials had included hundreds rather than thousands of patients. But respondents indicated how this then became the benchmark for subsequent trials.

***We only actually used two or three studies at the time of that launch. The most pivotal of which was the Tollefson data**. I recall at the time it was the **biggest ever study undertaken on a psychiatric population** (CS2.2).*

***Trials and guidance do influence, well, trials do. Mega trials are very important in terms of getting the opinion leaders to buy into the science quite frankly** (CS1.3).*

The 4S megatrial in simvastatin that was notoriously attributed to changing the way coronary heart disease was managed involved over 4,000 patients, but these numbers were necessary to prove an effect in clinically relevant outcomes such as morbidity and mortality, which was the unique feature that this trial offered.

***What was going to change the cholesterol lowering market were big trials**. If ever there was an area that is characterised by there having been an impact of big randomised controlled trials, it's this area,*

so I think it was 1994 that the ***first sort of big landmark study came out, the 4S study, and there for the first time was a demonstrated impact on total mortality, not cardiovascular mortality, but total mortality*** *in a population of middle aged men with existing heart disease and I think that was the* ***turning point at which people started to really kind of, sit up and take notice****. I mean there* ***had been pretty good evidence beforehand, but not in such a simple, elegantly designed, big trial as happened then*** *and I think you really start to see from the back end of '94 that things really start to take off (CS4.1).*

Large scale trials do carry weight but I think the problem is that as soon as they carry some weight they also become the next benchmark *(CS1.2).*

In addition to intimidating the competition with trial size, respondents suggested how insightful trial design can also provide a means of managing the impact of competitors. Clinical trials are expensive to conduct and therefore their design and magnitude are related to the resource allocation provided by the manufacturer. Respondents discussed how companies that are in a position to allocate substantial resources to their clinical trial programmes can generate what is effectively an 'evidence barrier' by conducting trials covering many possible patient group scenarios. This was demonstrated in the PDE5 inhibitor case, where Pfizer from the outset conducted studies in multiple patient groups, and in doing so raised the bar in terms of the evidence level required, forcing its competitors to compete on a much more uneven playing field.

The thing that Pfizer did very well I think was, ***we studied Viagra in everyone****. This is the point, this is where the evidence I think became increasingly important because* ***we could say, here's our data on diabetes, here's our data in spinal cord injury and you know, psychological cases, and no competitor during that period was ever going to have anything like that****. It showed its effectiveness, but it also* ***forces people to compete across loads of different areas, which is very difficult for them to do and raises the cost of entry*** *so we were always going to have a very high market share, you know, very early on (CS3/ INT1).*

3.2.2. Evidence translation: Relevance/limitations of trial outcomes

For evidence to impact on prescribing decisions an analysis of Industry views suggests they believe the trial outcomes firstly have to address the clinical needs of

prescribers, and secondly have to be translated into a usable form with meaning consistent and relevant to their clinical practice.

3.2.2.1. Head to head comparisons

When there are several competitors in the market, there is usually a desire from the clinical community for head to head comparison trials. The importance of comparative trials was a factor that was raised by most respondents during the interviews. Their view suggested that those companies that design their trials to try and meet the needs of prescribers are likely to have a greater impact. However, it is unsurprising that respondents indicated a reluctance from companies to conduct head to head trials according to what is often termed 'clinically relevant' outcomes unless there is likely to be a clear advantage of one drug coming out ahead of another. There was the suggestion that when there is a limited time frame in which to recoup the costs of R&D, then to conduct a head to head trial that may consume the remaining half of the patent life (which would be the case in a condition like osteoporosis to demonstrate a reduction in fracture risk), is not financially viable for a company and would be detrimental to the drug's diffusion whilst waiting for the outcome.

> *Our cost of entry is becoming increasingly higher and there's* ***not going to be a head-to-head trial on hip fracture between any drugs, because when they all work as well as all of these do you're talking about 50,000 patients, five years before you even stand a chance of seeing any difference****, and when you see the difference it's* ***unlikely to be clinically that significant and meaningful to actually knock one out of the market and favour the other*** *(CS1.2).*

For first entrants, head to head trials may involve drugs from a different class if that class represents the current standard of care. Respondents described the challenge this sometimes poses in ensuring the right agent at the right dose is used as a comparator given the variation in clinical practice internationally. In circumstances

where the comparator is not relevant to the UK, respondents suggested that clinicians have to make a judgement as to the likely impact of the difference. Once a class has become established the use of intra-class trials becomes more relevant as differences on which to prove relative advantage become less apparent. The onus then usually lies with later entrants to provide the data. If two drugs are being developed in close proximity, comparative data may not be available for several years after they reach the market.

*At that time we had **no head to head data** versus risperidone. The **differentiation was against the typical antipsychotics, notably haloperidol** which did present some problems in the UK because **haloperidol, although the standard of care in the US, is less commonly used in the UK** and indeed across much of Europe. So haloperidol was really **seen as a proxy for typical antipsychotics and people were left to draw their own conclusions about what that meant against their own personal standard of care**. Be that another typical, such as chlorpromazine or against risperidone. But I remember one of the great needs and the **great pleas from our sales forces at the time was we need head to head data versus risperidone** which we simply didn't have (CS2.2).*

***It's sometimes quite difficult to work out what your comparators need to be**. In some therapy areas, **standard care in other countries is now not the same standard of care in the UK**, so that in itself is proving quite problematic. **What we're starting to see in the UK is divergence of clinical practice from the rest of Europe** so from some therapy areas potentially oncology, the drugs that are now standard in the rest of Europe are not standard in the UK so…it becomes incredibly expensive, I mean the **clinical trials are tremendously expensive to run and it can be quite difficult if you were having to run them for individual countries**, and they cost £30 million, £40 million a trial, and you're never going to make the money back (G1.1).*

Despite several head to head PDE5 inhibitor preference studies (patient preference being the only basis on which any new entrant could attempt to compete with such a dominant first in class), methodological issues compromised the validity of the study results. Even a preference study designed to counteract these issues did not cause a change in behavior, indicating the importance of other factors in this case. Respondents believed that this brings into question the utility of comparative data, which is both expensive and time consuming to generate, for if it does not align with clinicians' experiences or beliefs, respondents consistently indicated it is unlikely to influence behaviour.

*There are a **whole load of different preference studies** which were being used at the time but they **all had methodological problems**. So **different doses comparing each other and different instructions** and all sorts of weird things going on (CS3.2).*

*If you actually look at the wealth of information out there I think **Viagra's got** something like, I don't know, **five, ten times more clinical papers than we have** on the sheer numbers of it. But if you **look at our numbers of head-to-head studies versus them** and if you looked at, say, preference, although each of the drugs have got some studies or abstracts which show a preference for one of the other, **there's probably more out there, both sponsored and independent, which would show a preference for tadalafil. But that hasn't swayed things** (CS3.2).*

In the statin case, despite the initial lack of head to head studies, Industry views suggested that clinicians filled this gap by comparing the outcomes of placebo-controlled studies as a proxy for a direct head to head trial. There is a risk however, that a drug may be at more of a disadvantage in this situation than it would be if it was part of a designed head to head trial, where conditions are controlled to provide a fairer comparison.

***MSD staked their place as market leader for many years really with the 4S trial**; they had what was probably of the available statins, the **most effective lipid lowerer and they had the evidence to say this drug saves lives** and I think, that's reflected in their usage relative to the others. The **other drugs were either later or less convincing with their trials**, so there was actually very good evidence for pravastatin, but **pravastatin probably published more landmark trials, through the nineties than Merck did behind simvastatin, but the drug was less effective at lowering cholesterol** and it was the **most effective drug in the market place that benefitted** (CS4.1).*

3.2.2.2. Surrogate markers versus clinically relevant outcomes

Surrogate markers as outcome measures were acknowledged by respondents as being controversial as links to clinically relevant outcomes may not be firmly established in certain disease areas. This was true of the osteoporosis field, where the link between increased bone mineral density and reduced fracture risk still remains uncertain.

In statins, it required trials that demonstrated clinically relevant outcomes of reduced all cause mortality and morbidity to be able to justify the link between LDL-C lowering and improved survival in coronary heart disease. Once this relationship had

been established, subsequent new entrants to the class could exploit surrogate endpoint evidence to demonstrate greater efficacy. While extrapolations to clinical outcomes cannot be claimed from surrogate endpoints, interview data suggested that tacit links may be sufficient if the argument has been proven by others in the class.

> ***Until evidence came of mortality benefits which came with the 4S study, there was very little treatment*** *even though we were saying, you know 'you need to treat, you need to treat', but* ***nobody believed until you got the evidence****. You* ***eventually got the evidence and the treatment paradigm changed overnight****, from flat to whoosh like this, and then just powered on to be the biggest market in the world. Well, you know, there's still massive under-treatment of that, even though it's the biggest selling drug (G1.2).*
>
> *You have to really ask the question do you believe that it's an LDL story or not? So* ***from 4S onwards every single statin trial that's come out has shown that lowering LDL cholesterol is beneficial****. So are you saying that one statin is a miracle drug, or are you saying it's really largely its ability to lower LDL cholesterol? Now if you look at all them together and say okay, then you have the ileal bypass trial (POSCH[18]), which* ***saved lives without any statins, by lowering LDL cholesterol****...And so* ***if you draw a line from the top to the bottom, you can plot all these trials on a line that basically shows you the lower the LDL cholesterol the better your outcome is. So that's your surrogate market argument. We can lower LDL cholesterol, we can prove it does things to atherosclerosis*** *(CS4.2).*
>
> ***Some physicians will be completely closed off in terms of if there's no clinical outcomes data*** *I'm not touching it, and that's fair enough.* ***Others are willing to accept that there's a relationship demonstrated in other studies*** *in the past between reducing cholesterol and reducing CV events. We have to be very careful in our marketing because we're only licensed for cholesterol.* ***We cannot imply in our marketing that Crestor (rosuvasatin) reduces CV events because that data has not been demonstrated.*** *We can* ***show evidence from other studies, but we have to clearly associate them with the drugs that were in those studies and say Crestor lowers cholesterol then it's up to them to make the link if they want to*** *(CS4.3).*

It may be perceived as an avoidance strategy of Industry not to use clinically relevant outcomes in trials, but respondents explained how surrogate markers at least provide some basis on which to compare drugs in view of the financial and time constraints imposed on Industry by a finite drug lifecycle. Where trials reporting clinically relevant outcomes can be produced in the lifetime of the patent, then their impact on diffusion can be valuable.

[18] The Program on Surgical control of Hyperlipidemias (POSCH trial) showed that the use of ileal bypass to reduce cholesterol levels resulted in marked cholesterol reductions and a significant reduction in cardiac events.

*It's very **difficult to do head-to-head trials to prove clinical difference** versus an existing field in a drug which you **need to do a three to six year study, in a massive population to be powered statistically** to prove anything. It's extremely difficult. So you've **got to find other markers**. In this case that's typically done through **bone mineral density which you can actually measure at a relatively short phase and see change**, and that would be typically what people will do to try and get an edge over each other (CS1.3).*

*Along came Lipitor, atorvastatin; more effective still and by the time we launched, in the **late nineties**…the kind of **medical world had made its mind up that cholesterol lowering was a good thing**, that there was probably a **class effect** at work here, so probably **all of the statins worked**, and so which one were you going to use, well you were going to use the ones which lowered the cholesterol the most, and that's what led to the early uptake of Lipitor. As our **clinical trial programme progressed**, we began to publish trials that indeed demonstrated that Lipitor shared the benefits and in fact may have a **greater effect on mortality than simvastatin did, and that's when you saw the real kind of take off** , through the early 2000s when there was the **confirmation that that additional cholesterol lowering did translate to real benefit** and of course, the period of sort of 2001 through to 2004 was enormous for us (CS4.1).*

A few respondents highlighted how outcome measures must also be recognisable to prescribers. This is a problem in some specialties more than others. In psychiatry, for example, a reduction in positive and negative syndrome scale (PANSS) score, while familiar to clinical trial investigators may be less tangible to a prescriber, compared with reduction in LDL-C levels in coronary heart disease, which is more widely understood. The implication is that even amongst specialists, the use of primary evidence (clinical trials) in formulating a behavioural change may just be the mainstay of a small percentage of innovators involved in clinical trials that have a full comprehension of the findings.

*I think **in psychiatry, I think you would struggle to identify a really ground breaking study that kind of meant people used atypicals instead of typicals**, one, because of the nature of the illness and the nature of how clinical trials are done. So when you measure, do a trial for a statin and you are measuring cholesterol, you have your **primary outcome measures** for that trial will be **things that doctors that are prescribing them, totally understand**. If I talk about a **PANSS score or a Weimers scale** or any of those scales they are kind of, **not artificial but they are a thing that is done in order to get clinical trial results** and not just by the industry but that's how you measure the effectiveness of the drugs. Your jobbing **day to day psychiatrist may not really understand exactly what a reduction in PANSS score means to a patient unless they are involved in clinical trial work** (CS2.3).*

3.2.3. Temporal impact of evidence

Views amongst respondents on the point at which data has sufficient impact to form what is considered to be 'evidence' i.e. whether the adopter is convinced to use the innovation, were varied.

> ***People go to conferences to get the latest stuff so they definitely take note of what's presented at meetings, but you can't beat peer review journal publications*** *(CS2.2).*
>
> *I think once an abstract's* ***presented at a conference everyone knows about it****. And you're just waiting for the manuscript to come out then. So I think once it's* ***presented at congress or it's presented in a journal at abstract stage that's when it becomes evidence****. People know it's coming anyway. So the people change their habits overnight (CS4.2).*

Interview data suggested that clinical trials do not always have an impact at the point of publication. Their significance may not be realised until other events take place at later stages of the lifecycle, which then bring a new perspective on the findings. This temporal bearing on evidence impact was demonstrated by MSD's Fracture Intervention Trial (FIT1). It was a mega-trial involving over 6,000 patients, investigating the effectiveness of alendronate as a once daily therapy. MSD had previous experience with the landmark 4S statin trial and so were aware of the requirements for a study to be well received. Respondents indicated however, that post-publication, the FIT1 trial did not achieve the level of impact in the UK that was expected of such a prestigious trial. Respondents perceived this to be a consequence of a combination of tolerability issues and opinion leadership loyalty to their competition (see Theme 2: Clinician/patient experience; subtheme 2.3.2: Safety warning/concerns and Theme 8: Key opinion leaders; subtheme 8.2: Hierarchical cascade of influence/peer credibility). With the introduction of the 70mg once weekly formulation some 4 years later, the FIT1 trial results were believed to regain their significance once adopters were able to link the effectiveness of the molecule

(as demonstrated by FIT1) to the new weekly formulation once smaller trials had demonstrated equivalence.

They were preferring to use alendronate maybe than the competition because they've ***got the fracture intervention trial plus other evidence, plus the 70 milligram formulation*** *(CS1.3).*

In contrast, the AA case study demonstrated the power of early conference level publication. While the ABPI Industry Code of Conduct restricts pre-marketing activities such as advertising using the drug's name, it is possible to publish clinical trial results in journals and present data at conferences. Full results from one of the pivotal trials in the AA case were presented a year before launch. Respondents believed this was responsible for fuelling the level of anticipation amongst psychiatrists that contributed to the drug's rapid uptake. Publication of the full trial a year later and subsequent head to head data was felt to merely serve to reinforce clinical experience already gained.

There was such a ***pent up demand*** *for this drug. I remember being at some of the* ***congresses where the phase III data were presented prior to its launch.*** *And it was* ***standing room only in some of the auditoria where the data were presented***. ***People really were excited about this***. *That it did represent a breakthrough (CS2.4).*

Analysis of the interview data suggested that most respondents felt clinical evidence can lose its impact for later entrants to a class as there becomes less to prove. Reforms to the prescribing environment with initiatives such as the Quality and Outcomes Framework can however, bring new significance and interest in the evidence for a late entrant if it has bearing on being able to meet the objectives set out in the policy. The impact of evidence is therefore heavily influenced by the environment in which is generated (see Theme 4: Health service/policy environments).

There's not much more evidence you can collect really because most of it's been done in terms of placebo controlled trials, most of it's been done now. It's ***mostly unethical to do the trials anymore***. ***So we're stuck***. *So* ***doing more and more trials is probably not the answer, pharmacoeconomics is***

the answer *I think. Make sure that your product is pharmacoeconomically positioned to take advantage of the health system as it is now (CS4.2).*

There was ***awareness of the clinical data before launch*** *and that it looked fairly strong.* ***Other things that were in place like the QOF which physicians were starting to get wind of which directly incentivises them to go and find patients who were eligible for statin therapy and to treat them to a certain level****, those two things together, that's some of the reason behind that (CS4.3).*

3.2.4. Journal quality/ Publication control

Analysis of respondents' views indicated that journal quality is not necessarily proportionally related to diffusion impact, as often indicated in the literature. While most respondents considered publication of study findings in one of the high impact factor journals would have a significant impact on the uptake of a drug, the case studies revealed certain incompatibilities with this perspective.

It's ***not really until you get a full blown publication, if you can in a prestigious journal, that would have the most impact, so, you know, if it was in like the Lancet, the BMJ,*** *the data published in those journals would have* ***more impact*** *than data published in a lesser renowned journal (CS2.1).*

Most of the major trial findings for the BPs for instance were published in some of the most prestigious medical journals, yet the one highlighted as being instrumental in changing the trajectory of the diffusion curve for alendronate was the study by Schnitzer *et al*. (2000) detailing the results of the once weekly dose published in what would be considered a comparatively low key journal with limited readership.

One respondent discussed how the restrictions imposed by prestigious journals were detrimental to the diffusion of their drug. The measures journals put in place to maintain prestige, such as embargos on gradual release of trial results can misalign with Industry aims of building awareness and anticipation for the drug. Additionally, the time taken for a large scale trial to reach completion, coupled with a lengthy peer-review process poses a substantial risk that any unique outcomes of the trial may be pre-empted by competitor products.

We were very heavily ***focused on securing a very credible publication for our hip fracture trial published in NEJM*** *and NEJM is still regarded as the highest impact factor publication, out of all the publications you can have. The* ***downside is that they're very fastidious about how things work****, so the first thing is that you* ***can't do the gradual release it has to be brand new to the world****, otherwise it never gets into NEJM, and so it puts a lot of* ***blocks on what you can do, because from a marketing point of view, we want to be able to build up to it, but they won't do that, and that's why they're so prestigious*** *(CS1.2).*

Respondents felt they were to some degree at the mercy of journals, giving rise to a sense of disempowerment in this aspect of the diffusion process. This theme interacts with several other themes, including how the journal restrictions impact on the clarity of the messages the Industry want to convey (see Theme 6: Communicating relative advantage; subtheme 6.2.1: Simplicity/clarity of message). The frequency of this predicament however, is likely to be low as it occurred mainly as a consequence of inexperience in trial design from lacking a classic pharmaceutical heritage.

The other element is that ***they shape the publication****, so actually it's from a technical point of view* ***it's not the best written publication, it doesn't do justice to the dataset*** *that supports the publication, but we again don't have a lot of say in that because* ***it's NEJM and they have a lot of say in what they want and how they want it written****. I think if we'd* ***gone for a slightly lower impact journal, I think we would have had a publication that was more reflective of the data*** *that we actually had, I mean I think we do make mistakes…. We had an issue that* ***we wanted to do too much in one trial****, so what we chose to do was we chose to have an over 80s group, and again a potentially big market, a potentially big unmet need, but we complicated it... And so I think that's* ***maybe our inexperience*** *(CS1.2).*

Interview data suggested how journal quality is often used as a proxy to determine how much kudos a company affords to criticisms about its product, and to decide the extent of their response as more prestigious publications tend to reach a wider audience and what they are presenting is viewed with credibility by prescribers.

It will depend on ***the quality of the study and where it's published as to whether we would react to it****. You've always got to look….you know we have to present lots of evidence for our products and so we tend to….if we get an* ***individual study*** *that comes out and* ***look at what is the body of evidence that either backs that study up or disagrees with that study, if it's a one off and there's loads disagreeing with it I probably wouldn't bother with it. If it's one of a series and I think longer term it's going to hurt the brand if we don't respond to it, then we'll go proactive and respond to it*** *(CS2.2).*

4. HEALTH SERVICE/POLICY ENVIRONMENTS

The health service and policy conditions governing the environment into which a new drug diffuses were raised by most respondents as an important influence on diffusion. Unlike some of the other diffusion factors discussed, decisions about public policy were viewed as being out of the control, if not the influence, of Industry. For the purposes of this discussion, 'health policy' is that under the direction of the Department of Health, whilst 'guidelines', which are the instruments through which policy becomes operationalised, emanate from organisations outside direct Government control (e.g. NICE, Royal College of Physicians etc.).

4.1. Health Policy Environment

4.1.1. Political priorities

The alignment of key commercial messages to defined national priorities was regarded by respondents as an opportunity to drive diffusion and adoption. At the point of development, while it is not certain what the political priorities will be at launch, the National Service Frameworks have identified such priorities for the NHS and any related guidance is seen as having enhanced significance. Respondents highlighted that where possible, drugs are endorsed by their ability to achieve the outcomes set by policy.

The BP case illustrated how the degree of political priority afforded to a disease area can dictate the impact of national guidance. Although a relevant policy document existed in the form of the NSF for Older People, osteoporosis was mentioned only as a feature of a subclause, rather than a major focus. From the respondents'

perspective, the effect of marginalising such issues diminished the potential impact of that policy.

> *It **wasn't on the government's agenda**, as it still isn't now, because even though the sales look terrific compared…it's still relatively low. If you look at the actual number of patients seen in a typical month, it's much lower than say for the A2As[19] and statins. Equally, when you look at the **different quality outcome framework measures** and the different disease areas which have been prioritised, **osteoporosis maintains a very low priority** compared to things like cholesterol and hypertension, and so I think it's still….it's not given the kudos and the priority that it needs (G1.2).*
>
> *I think the overall driver is **how important is this a priority for the health services** that we work in? So you know, if you take something like say a statin, where clearly **now a lot of the focus** of the overall health service is on **statins, and prevention of coronary heart disease**, then a **national guideline in that area is likely to get a lot of traction and be a very major event in the diffusion curve of the drug** or how it's adopted. **If you've got another area that's probably much further down on the political medical radar and it gets much less priority then even if you get a national piece of guidance on it, it can drop a little bit by the wayside**. **Osteoporosis** is not a bad example, because if you look at it in terms of the national guidelines, it is **covered by an NSF but it's a subclause of the NSF for the elderly and a subclause of falls and fractures** which then leads you to, okay yes there's a national piece of guidance there saying…we need to do something about this, but it's **not sufficiently high enough up anyone's agenda to really make a difference**. So whilst it could be the trump card in terms of what changes the adoption of a particular class of drugs, it will only be that if it reaches a certain critical mass that gets it there (CS1.1).*

The NSF for Mental Health was believed to have had little impact on the AAs. While it outlined best practice, the means to implement the changes were not considered to be a high political priority. In contrast, erectile dysfunction, which had not been regarded as a political priority, was elevated to the forefront of the political agenda with the development of the first oral PDE5 inhibitor sildenafil, due to fears of the projected uptake costs to the NHS. Interview data suggested that while this drug raised the profile of ED, the provision of services for the condition did not become a political priority and as such, related policy as represented in the NSF for Diabetes (a recognised cause of ED), did not have a significant impact on the management of patients with ED. If a condition has symptoms that straddle several government priority areas, in some contexts respondents perceived that this can be used as a

[19] Angiotensin II antagonists

means of deflecting accountability from the issue becoming any one service's responsibility.

> ***NSF was not very useful***. ***Lots of best practice*** *and that's what we should do but not a lot to really help the NHS make those changes.* ***Interesting documents*** *to read, you know, good visions for where they need to be* ***but then you've got to make it happen on the ground*** *haven't you (CS2.2).*
>
> ***How many diabetes centres as a result of the NSF for diabetes now run ED clinics****? And how willing to proactively to turn round to all their diabetic men and openly talk about ED?* ***We've generally found you almost get good centres and bad centres*** *and I'm not doing them a disservice in that, but you generally find that they will move...that they're almost* ***forward thinking*** *or they believe that yes, this is a cause of it, you know, diabetes...****we will treat this like we treat people's feet and their eyes and everything else that diabetes impacts on****. This is just another part of the disease, because it's a vascular disease, so let's deal with it. And you'll get* ***other centres which will say well that's a urological problem****, isn't it? Yes there's a link obviously with diabetes but we'll refer patients over to deal with ED. I'm not saying one service is better than the other but you look at it from a patient's point of view and if I'm a diabetic man and I come for treatment and they check my eyes in that clinic or even check my feet but then they do nothing about my ED. They'll say, you know, 'Any problems down there? If so, go speak to my colleague'. So* ***policy in that respect hasn't seemed to have had a huge impact****...which is very, very unfortunate. I mean 50% of diabetic men over 18 will have ED (CS3.2).*

4.1.1.1. Favourable policy environment

Several respondents indicated that policy resulting in the new General Medical Services (GMS) contract was instrumental in setting the health priorities in primary care. Technologies that can be linked to meeting the Quality Outcomes Framework (QOF) indicators are introduced into a receptive environment resulting from established, albeit incentivised clinician interest. This was identified as one of the important factors in driving use of statins. Drugs unrelated to the QOF can potentially face an infrastructural barrier to diffusion. This was proposed by respondents as being detrimental for BPs, as osteoporosis indicators were not included in the original QOF, only later being added in April 2012 when all three case study drugs were off patent.

> *I think if we said what is the one thing* ***aside from the availability of clinical evidence*** *that has* ***driven the use of statins*** *in this country; you would probably say* ***it was the GP contract****. That's not so much a guideline, that's a financial incentive to do something (CS4.1).*

*The **physicians were starting to get geared up for the QOF and the GMS** at the beginning of 2004 and therefore **having good LDL and total cholesterol data** perhaps it was a **favourable time to have that** with where the focus…**where the minds were starting to move**…There was recognition that statins should, could be used more widely, as well as things like the **QOF which incentivised physicians to go out and find patients who would be appropriate for statin therapy** (CS4.3).*

*There are different barriers of access, and GPs are busy and the **GP contract has changed things** because I mean they're very **focused about getting their points** (CS1.3).*

*There's a relationship between the NSF and QOF and **once you've got cholesterol indicators in the QOF and you've got indicators around creating disease registers**, and **patients having to have cholesterol readings, then that's going to drive use** (CS4.3).*

This approach however, does not appear to be immune from wider commercial influences. The QOF, once a driver for diffusion of branded statins, was later perceived by respondents as a barrier with the introduction of cheaper, generic simvastatin.

*I think you had a sort of cumulative effect of several things, going back so that certainly the **NSF , really kind of put this on the map, cholesterol, heart disease prevention through cholesterol lowering**. The first **GP contract of course then gave QOF points** for treating cholesterol and that certainly **pushed the market** again, very good thing too, right thing for patients. I think the **NICE guidance** of, when was it, beginning of '06 has had a **positive effect on continuing to boost statin usage** in primary prevention as opposed to just in secondary prevention although, commercially we probably haven't benefited from that because it's been **the cheap generic statins** that have tended to be used in those lower risk patients, so I would say yes, the **things that have had the big effect have been NSF and GP contract** (CS4.1).*

4.1.1.2. Adverse policy environment

Analysis of respondents' views suggested that policy can provide the justification for prescribing restrictions purely on the basis of cost containment when the decision cannot be made on clinical grounds. In the case of the PDE5 inhibitors, policy presented a major barrier to diffusion by restricting their use to subpopulations with certain comorbidities, whilst also excluding the most significant of these subpopulations (cardiovascular disease) as it presented a major opportunity cost threat to other prioritised areas (e.g. cancer).

*They **reviewed Schedule 2 just prior to tadalafil and vardenafil launching**, and they had over 200 responses of which only one said, don't increase the categories of patients, all the other 199 or **200 said you should include patients with cardiovascular disease, because the link between erectile dysfunction and cardiovascular disease is a perfect link** almost, but the Department of Health then said, whilst we've had all this feedback to say change the categories and that and add cardiovascular patients, to do that, we **would have to take money from cancer treatment**…There is a huge link between cardiovascular disease and ED. I mean still, it's **unfair** that they were you know, picked out rather than patients with diabetes, it's **almost like you want to get diabetes as well, because at least then you'd get your treatment on the NHS** (CS3.3).*

***Schedule 2 reduced the number of people that had free, or NHS access to it**, to about 40% or something like that from the volume that you would have otherwise have had. Now you know, some people will pay for it privately, but you know as a **nation we are not very good at paying for our medicines** unless they're pretty vitamins in which case, no problem at all, but you know, we don't really like paying prescription charges, we certainly don't want to be paying £40 for a pack of Viagra, **so inevitably it will limit it** (CS3.1).*

Respondents perceived such policies as creating confusion for patients and discomfort for their doctors in having to manage the prospect of discrimination without sound clinical grounds. This links back to clinician experience (see Theme 2: Clinician/patient experience; subtheme 2.2: Clinician-patient interaction), for while the oral mode of administration of sildenafil enhanced the clinician-patient interaction, the policy restrictions counteracted it.

*We should either **make men pay for this drug or provide it on the NHS, one or the other** and the reason why I say that is for a clinician, what they've said is it's very **difficult to explain to a patient 'Yes, you qualify' or 'No, you don't** but here's the reason why'. And the guy says 'Well, so hang on a second, say I had **coronary heart disease** because I'm overweight and I've eaten too much'. 'Yes you do **have to pay for it**.' 'Okay, but if I had **diabetes** and I had diabetes because again perhaps I was overweight and I'd eaten too much and abused myself that way, do **I qualify for it?**' 'Yes.' That's a difficult thing for clinicians to be able to explain and so their feedback is that they'd prefer it one way or the other, 'cos it **feels like they're discriminating** (CS3.2).*

Policy restrictions that challenge a clinician's autonomy in the clinical decision making process were viewed as not being generally well received and can have unpredictable consequences on diffusion. In the case of the PDE5 inhibitors, interview data suggested that the initial outright ban on the use of sildenafil, was met with defiance from clinicians as an infringement to their profession prescribing freedoms, which are essential to enable them to gain experience with new drugs (see

Theme 2: Clinician/patient experience). When the restrictions were lessened to those under Schedule 2, the Industry respondents believed specialists often took a pragmatic approach and used the ambiguity of one of the permitted exclusions of men suffering 'severe distress' on account of their ED, as a means of widening access to the drug and reducing discriminatory barriers.

*Contrary to the **NHS being free healthcare at the point of delivery according to clinical need,** I mean that was a pretty **sacrosanct principle** and still is in effect, and **this was a very high profile contravention of that for a drug which people knew was effective**, so again clarifying that was not in debate. It wasn't like this sort of vague notion of efficacy, **it worked in 70-80% of people** on average, and **it was safe**, you know and to all intents and purposes it **wasn't expensive**. It was £5 a tablet, so that's £20 a month and that was absolutely in the middle or the lower end of what most monthly medicine costs, so there was **no reason to ban it, other than a fear about its uptake**. So anyway, we contested that, it was lifted, but what was put in its place was Schedule 11 which is now **Schedule 2**, which when it was **reimbursed it was only for people with; the largest group was diabetes**, so new patients presenting with diabetes could have it, and then there was a whole load of lesser conditions…there were twelve, so **multiple sclerosis, motor neurone disease, spinal cord injuries, radical prostatectomy, transurethral resection of the prostate**. But the one which was the **confusing one for people, which wasn't helpful actually, was that anybody that was experiencing severe distress** as a consequence of their erectile dysfunction as diagnosed by a specialist, of course that was very much in the eye of the beholder. I would say there were probably about **20 GPs who were experts in the area all pretty much took a view that if you were; if you had plucked up enough courage to go and see a GP about erectile dysfunction, you were probably pretty distressed by it and therefore, qualified** (CS3.1).*

*I think, **Schedule 11 was designed to do something other than what it was subsequently used to do with Viagra**, it was something to do with where a drug has two indications and its only approved for use on the NHS in one indication but not the other, whereas with Viagra, they used it to say okay, only with certain aetiologies...so **Frank Dobson said you cannot use it**, and that was his guidance to the medical community on the basis that it **was going to cost a billion pounds**…And of course a lot of people as you can see from the take off curve, **a lot of people ignored that and it produced a pretty big reaction from, obviously Pfizer, but also the BMA**; I mean influentially we have no links with the BMA, the BMA is entirely independent, but they just thought that **was an infringement of GPs' rights**; their professional freedoms (CS3.1).*

4.2. Independent Guidance/Guidelines

Guidance or guidelines provide the conduit through which policy aims can be implemented in clinical practice. They are used to influence the environment, either as barriers or enhancers of diffusion depending on the central message. In the PDE5 inhibitor case, respondents discussed how guidelines had little impact other than to clarify how simple the condition was to manage, which aimed to encourage the

transition from prescribing in secondary to primary care. In the BP case, guidelines were produced too late once practice was already established. For the AAs, guidance had little impact for the individual drugs as it did not attempt to differentiate between products, but did enhance a collectively positive message for the class. In the statin case, guidelines encouraged more extensive use of statins, but the market had become generic at the point when the NICE appraisal was produced, and so the respondents believed they did not benefit from the increased use.

4.2.1. Differentiation

Analysis of respondents' views indicated they had mixed feelings when guidelines considered technologies as having a 'class effect'. Class endorsement by key opinion leaders was seen to be useful in early stages of diffusion to initiate a shift in clinical perceptions towards a new class (see Theme 8: Key opinion leaders; subtheme 8.3: Collegiate agreement). Guidelines however, may only materialise late in the diffusion process once experience has formed opinion regarding class function, and what is sought is advice on differentiation within the class to assist in prescribing decisions. Respondents acknowledged that while a positive guideline recommendation of a class at this stage is helpful, impact stems from drug-specific endorsement.

NICE guidance for instance on the AAs achieved a positive message for the class, stating they should be used in preference to the older generation drugs, but it did not go so far as to distinguish between them. Respondents therefore felt it had a diluted impact on the diffusion of the individual drugs within the class. The same was true for guidelines on the PDE5 inhibitors where the main focus was not to differentiate

between the PDE5 inhibitors, but rather to ensure they were prescribed in the most appropriate clinical setting.

*I think **guidelines were useful in terms of driving the class of atypicals** because the guidance recommended that atypicals for new patients should be considered as first-line treatment, or patients that were on older conventionals who had side effects should be considered for a change to atypicals, so I think as a class it helped to drive the atypical class, but it **didn't really go into the detail of specifying differences** between the different products, so I **don't think it made any difference to the individual products**, it was more driving the atypical class (CS2.1).*

*Guidelines in ED are rare, they tend to be local, and they're driven by the urologist in order to manage their waiting lists. From what I've seen from the vast **majority of guidelines are; ED is easily treatable in the majority of cases with a tablet and can be done so in the community**. You should only be referring patients into the urology department if they've tried eight to 12 successive tablets and failed, so then they may need an injectable or something like that which tends to be initiated within the secondary care arena, so **most of the guidelines I've seen have just said any PDE5 inhibitor, but in the community please** and then when you've **tried several times and it doesn't work, then you have permission to refer** that patient (CS3.3).*

For some drugs in a class the implied nature of equivalence from a class effect guideline was perceived to be advantageous, particularly if it has been subject to perception issues of reduced efficacy, as in the case of quetiapine. Equally, a lack of guideline differentiation can be beneficial in circumstances where one drug may have a less favourable side effect profile by diluting its impact.

*We then moved away from that later to just really focusing on efficacy, let's not try and change it, let's just convince them that actually, **just like NICE says, Seroquel is equally as good** as olanzapine or risperidone, because **NICE says they all work exactly the same** (CS2.3).*

Interview data did confirm however, that where guidelines indicate a degree of differentiation, these opportunities are maximally utilised in Industry messaging to indicate it as the drug of choice in a particular situation that has been endorsed by independent validation (see Theme 6: Communicating relative advantage; subtheme 6.1: Differentiating relative advantage).

*What **NICE** did do though was **say there was a need for atypicals** and that **from our perspective is a good message**. You still have a lot of typical use going on here…they are an advance, atypical antipsychotics, we should be thinking of using them 'cos the older typicals had and still do have very serious side effects, so that message helps us. **NICE guidelines that followed the guidance** they **did***

differentiate on drugs and olanzapine for instance….was pulled out for *crisis in the wards,* ***rapid tranquilisation****. And then that way* ***that does help us*** *because you can then actually use that to say* ***olanzapine has been the drug of choice in this situation*** *(CS2.2).*

Guidance rarely endorses individual drugs, but the use of language within the recommendations such as 'lowest acquisition cost' will favour the cheapest in that class and in doing so imposes a degree of differentiation. In a market of branded medicines, some respondents indicated that there remains scope for competitive pricing, but in a market that has become generic, this recommendation does little for the diffusion of branded drugs in the class.

NICE TA stated that statin therapy as appropriate *for people who have established cardiovascular disease, who have events or evidence of cardiovascular disease, but also those who are deemed to be at greater than 20% ten year risk of developing a cardiovascular disease over the next ten years, that was the first outcome. The second was* ***therapy should usually be initiated using a low cost statin*** *which* ***generally means simvastatin or pravastatin*** *(CS4.3).*

4.2.2. Perceived importance/strength of message

The impact of clinical guidelines was perceived by respondents as being related to the credibility of the source of the guidelines and the strength and clarity of the message being conveyed.

*We tend to look at sort of prescribing behaviour on a macro scale and say '****did the guidelines change behaviou****r?' I think* ***it's how dramatic they are*** *(CS1.3).*

Very strong ***recommendations from NICE*** *I think, but it* ***depends on the wording and how strong it is****, so I think the fact that they were positive about atypicals did have an impact (CS2.1).*

There is seen to be a clear hierarchy of guidelines with NICE at the apex, due to the credibility with which this organisation is viewed worldwide and the mandatory authority of its appraisals. Guidelines from Royal Colleges are also held within high regard within their respective fields, but when, as in the case of BPs, they are very closely associated with developers of the technology, doubts about wider credibility are inevitably raised.

*So **would we all be supporters of the Royal College guidelines**? **Yes**. So did all of us as in every single company that was in the osteoporosis field, pharmaceutical company or diagnostic company. All of them have to be supportive of the Royal College guidelines, because it **is the national guideline for the UK for those products** (CS1.1).*

*The prescribing incentive schemes, like the league tables, the better care, the better value indicators in some of the software, were borne out of that NICE TA guidance if you like. That **guidance gave a lot of local prescribing advisors the ammunition they needed to try and do what they were doing anyway**, which is try simvastatin. I mean you can argue, might some of that stuff have happened anyway without the NICE guidance? Possibly. But in terms of the timing of it, **a lot of those tools seemed to come into place in 2006 and that technology appraisal for statins was published** at the beginning of 2006…I think it's fair to say it's had an impact definitely (CS4.3).*

Irrespective of the weight of importance of some guidelines, respondents suggested that affordability and whether the recommendations are commensurate with clinicians' personal beliefs will still present a barrier to guideline adoption and their subsequent influence on clinical practice. In the statins case, respondents felt that the Joint British Society guidelines (JBS2) that supported lowering cholesterol targets chimed more with clinical practice than government policy. Such was the clinical support for these guidelines, it required Department of Health intervention to clarify that these guidelines were not commensurate with national policy.

*A lot of people **don't even follow guidelines anyway**, I mean you can have the best written guidelines in the world, but **whether they can afford them** and whether they **believe that that's what they should do** is something entirely different (G1.1).*

*In terms of policies, I guess you would assume that those have been influenced by the data. And other things have been important, the **Joint British Societies' collection of professional bodies; their guidelines** have been useful in that they've reminded people that, with the need to **treat more aggressive cholesterol lowering targets**, those have never been adopted to date by Government as policy, but I think, **many Physicians view them** as probably representing the **gold standard** of treatment (CS4.1).*

4.2.3. Timeliness

By their very nature, the advisory capacity of clinical guidelines is dependent on data which may not be available until products have become established. The same paradox is true for systematic reviews. Respondents indicated how this may limit their value in accelerating diffusion as experiential use has usually gone some way to

informing clinician opinions by then. Some interview data almost trivialised the impact of guidelines, suggesting that conference or abstract material has far greater potential to impact on diffusion by aiding a more rapid uptake of the product during the early phases.

*The fact that **NICE Guidance** was **produced relatively late in the lifecycle** meant that **impact on people's prescribing habits was probably fairly limited**. Had they **come along three or four years earlier** than they did then it **might be a different answer**, but they came along so late in the lifecycle (CS2.2).*

***If something about a statin came out in abstract form next week at congress it'd change the policy overnight, without waiting for the guidelines** (CS4.2).*

Producers of guidance, especially NICE, need to ensure that they retain high quality standards. This invariably increases the time to publish and, arguably reduces the usefulness of their outputs, which was highlighted by respondents as a particular issue for the BPs. The RCP guidelines published much earlier were perceived by respondents as having had a greater influence on prescribing behaviour.

*Then you've got **NICE** which **can take many many years**, as osteoporosis has done. And it's a bit embarrassing because the length of time it's taken, so **many events have taken place it's made everything they've done redundant** (CS1.3).*

Respondents agreed on how timing of guidance production can give rise to unfair advantages to some drugs in a comparative analysis. Later entrants to the market may be discriminated against by guidelines as the compounds will not carry the same weight of evidence as that first to launch. This was a particular issue for the PDE5 inhibitors when the class was subject to review by the Drugs and Therapeutics Bulletin within a year of tadalafil and vardenafil being launched, while sildenafil had in excess of six years data.

*The **Drugs and Therapeutics Bulletin did a review**, and I think both Levitra **and Cialis were probably only about a year post-launch**, if not, less than that, so whilst we had one or two studies that were fully published, we didn't have lots and they **reviewed all three PDE5 inhibitors**. Now the Drugs and Therapeutics Bulletin will not accept abstracts or posters from meetings, they only accept peer-reviewed published papers, so **automatically they're advantaging Viagra**, and they came out and said there's **no reason to prescribe either of the two new ones**, because the **bulk of the data is with Viagra. Well it would be, it's the oldest treatment** (CS3.3).*

In contrast, a late entrant from a different class in the statin case was considered at an advantage by respondents, as consensus thought in the field had advanced such that evidence requirements may not have been as stringent as for drugs assessed at earlier stages.

*Extremely surprised how NICE reacted to it. When they did the statin one, they said it **was important to have endpoint evidence for statins**. When they did the **ezetimibe one they said the LDL theory is now proven**. It's like, okay, **18 months down the line the whole world's changed** it seems, which I thought was a bit out of kilter to where they position themselves in terms of evidence (CS4.2).*

4.3. Health Service Environment

4.3.1. Clinical priorities

In contrast to political priorities, clinical priorities focus on the needs of patients, but are not free from financial considerations. While conditions, such as erectile dysfunction, can cause considerable distress to a patient, analysis of respondents' views indicated that when it comes down to prioritising resources, the clinical priority is for innovations that are life-saving rather than life-modifying.

*The other thing that happens is, in some areas the clinic is funded by the PCT, but then part way through the year when the funding starts to look like it's; you know the **money is not going to stretch to cover everything**, it's the **ED services that get pulled**, because they're **considered non-essential**; **no-one's ever going to die of having an erection problem, or that's what people believe**, although some people have tried suicide, but that's extremely rare; people will die of cardiovascular disease or cancer but people don't die from having erection problems, so therefore, **they'll pull the funding back on erection services to maintain some funding in another area that they see as more critical** (CS3.3).*

***Do we spend money on cancer care or on people's sex lives**; well you know, **put like that it's a difficult question to answer**, but I mean you know the **important thing that we had to get across was, look, this is a real condition** (CS3.1).*

Respondents in the BP case described how for some diseases, such as osteoporosis, a vicious circle ensues. Lack of political attention means a lack of clinical prioritisation, which results in limited resources. In such circumstances respondents indicated how they aim to raise disease profiles that would otherwise find it difficult to draw attention away from major clinical priority areas such as cardiovascular disease and cancer (see Theme 7: Market development; subtheme 7.2: Raising disease awareness).

*It **wasn't actively being supported by the key opinion leader community in the hospital** so they would be sending people out, but it was fairly minimal. So even in fracture clinics there was under-diagnoses, there was also a **lack of facilities available**, such as DEXA scanning across the country, so **lack of resources to actually actively look for and identify people** who were just osteopaenic for instance, and you know, early stages of the disease (G1.2).*

*I think again it's an area where the **lack of understanding in the market amongst the customers was very high**, so even the GPs, their knowledge of osteoporosis, their ability to be able to actively diagnose or identify an issue. And their **desire and their willingness to do so was actually really low** (G1.2).*

With the resources that are available, there is significant pressure to utilise them in the most efficient way. In the statin case, the clinical priority was to reach cholesterol targets set out in the QOF, but in the most cost effective way so that more patients could be treated. This was achieved through generics, which ultimately curtailed the diffusion of branded drugs.

*Universally **every local PCT, LHB[20], has a guideline formulary in place** which says **simvastatin is first-line** and that undoubtedly has an impact on this with all the kind of infrastructure that goes with it. You've got the better care, better value indicators as well. So there's a lot of **infrastructure around driving proportionate statin use that is generic**. Incentive **schemes that's a good way to get physicians to do what you want**, prescribing incentive schemes, league tables, there's the ScriptSwitch software on clinical systems…it's a service that the PCT can buy in to drive the prescribing that they want, for example if where you had the ScriptSwitch software in place for a GP to prescribe atorvastatin it would flash up, I'd get a window flash up and say actually do you realise that local policy is to use simvastatin? And it would default to simvar and create an exception report if you chose to override it to write atorvastatin. So there's those kind of **point of prescription influences** as well as the things that go on in the background (CS4.3).*

[20] Local Health Board

4.3.2. Clinical setting of disease management (specialist/non-specialist)

The complexities of the clinical setting in which prescribing takes place can have a bearing on diffusion. Respondents highlighted how in mental health, local variations in how services are configured can make it difficult for them to determine who are the key people that influence practice. This can result in a dilution of Industry efforts compared with conditions managed predominantly by GPs within primary care, such as statins.

> ***In mental health*** *the structure can be very different from one area to another. So in some areas there are moves generally to move patients out into primary care faster, because* ***traditionally they've been managed in hospitals, kept in hospitals for perhaps, you know, four to five months****, and then they've been discharged back into the community but looked after by mental health trusts. There are* ***moves to change that, to keep the stay in hospital much shorter,*** *so bring it down to perhaps a month or so, six weeks,* ***discharge the patient faster back into the community*** *and then they'll be looked after by nurses in the community, so mental health nurses, but that would be* ***funded by the PCT, so it is all shifting****, but mental health is - has quite a fragmented structure, so you can literally* ***go from one area of the country twenty miles to another area, and the way that mental health services are set up can be completely different****, and that* ***makes it quite hard to deal with the primary and secondary care interface*** *because you've got to* ***deal with it on very much a local level*** *(CS2.1).*
>
> *There was* ***enough knowledge around statins for GPs to be really comfortable with them****. It was* ***generally a primary care managed disease and by exception you send them to secondary****, and as I said because of the sheer number of patients, that's the way it has to work, so the* ***marketing was both to primary and secondary care*** *(CS4.3).*

This was also demonstrated in the PDE5 inhibitor case. Despite significant market research ahead of launch, interview data suggested later entrants to the market may not have appreciated the continuing importance of secondary care specialists in influencing prescribing decisions as a result of the focus placed by the first in class on shifting the management of erectile dysfunction into primary care.

> *We* ***scaled back our specialist care sales force…*** *because* ***we believed that primary care was where everything was at****. But* ***although 98% of the prescriptions are maintained in primary care****, a third of them...there's a point where* ***the specialists get involved in certain numbers of the patients and so those specialists are the ones who then advise the GPs,*** *so then you've got a combination between the two back in here, because we're back into specialist care (CS3.2).*

The importance of national guidance was conceptualised by respondents as being related to the care setting in which a condition was predominantly managed. Respondents suggested that they are seen to be more significant for conditions that are managed predominantly in primary care by providing a framework for ensuring consistency in practice, thereby instilling a degree of confidence for non-specialists (see Theme 5: Adopter Attitude; subtheme 5.3: Non-specialist risk mitigation). There was a perception amongst respondents that specialists were seen to have achieved a level of autonomy, which allowed them to prescribe as they saw fit.

The impact of the clinical setting was an important feature in the PDE5 inhibitor case study. Mode of administration of drugs can generate a barrier by restricting innovations to certain clinical settings. The development of an oral medication for ED that did not require specialist administration was perceived by respondents as a critical success factor for this class of drugs. It enabled the movement of the management of ED out of secondary care into a primary care setting. As there are far more GPs than urologists, this ultimately translated to increasing the number of patients that could be treated and the ceiling of the diffusion curve could be raised. The policy restrictions however, forced prescribing decisions regarding initiation of treatment back into the realms of specialists.

*There were probably three or four things that we were focusing on in the sort of two year run up. One was, **how do we get GPs equipped for the arrival of Viagra**, which was; it had two aspects to it; both commercial, but one almost had; well actually had a responsibility because **erectile dysfunction** which as you know was **primarily treated using injections, was entirely secondary care**, pretty much entirely secondary care focused, apart from some primary care clinics, and **we knew that patients would turn up in thousands at GPs door steps saying please can I have Viagra**, you know that was absolutely certain, and so as well as it being **in our interest to move the management of erectile dysfunction into primary care because there's 40,000 GPs and there's only 2,000 urologists**, it was also in the interests of patients who didn't have to go and see the urologist, but it was also responsible for GPs to be expecting that and have some sort of training. So a **very significant effort** was around, **how do we make that shift with management into primary care** (CS3.1).*

While the change of formulation may have addressed a physical barrier to widening access, some respondents believed a social barrier was created by losing a degree of specialist involvement. Specialists are the ones who tend to drive interest in new therapies and without their involvement this may have affected adoption of subsequent PDE5 inhibitors by compromising the choice of treatment options presented to patients. One respondent felt this was a particular issue for the second in class, as an appreciation of the additional benefits it brought to patients was not necessarily recognised and communicated by non-specialists.

*If you look at the numbers of **specialists,** there's maybe 1,000 that will have a clinic run in their department or under them that a nurse may lead with a specialist registrar that they're responsible for. So **they'll see a number of those patients all in one go**. They **actually have an interest** as well, because 'it is a consequence of the prostate surgery which I perform therefore **I could do more about this** and men **will come back to me and constantly talk to me about it'**. Whereas if I'm a **GP** and I **see one new patient every two months, what are my interest levels going to be**? (CS3.2).*

*The **physicians that are interested offered the choice** and said 'Okay Mr Jones, you have erectile dysfunction, you have pretty much two options. You've got **Viagra**, you've probably heard of. **This is how to take, this is what you do. Think about your sex life for that. Or here's Cialis. This is how you take it again, you know. Think about your sex life. This is what it could do for you.'** That's a **true offer of choice** between the two. What you found **a lot of physicians did on the offer of choice was to say there's long-acting and short-acting, what do you want? That's very different.** So a lot of it was around... **giving a true offering of choice. Specialists get that a lot quicker** than GPs because they treat more people. They **hear more of the impact of ED** on that person's life (CS3.2).*

4.4. Industry Response to Environment Barriers

Conversion of policy objectives to Industry aim

Interview data highlighted the reflexive responses of pharmaceutical companies to the policy environment. If the focus of a guideline or policy is not commensurate with a company's message, or the content is ambiguous, respondents discussed how attempts are made to draw attention to issues, such that their interests are represented. The aim is to subtly influence policy by providing a link, however tenuous, between the policy objectives and the pharmaceutical intervention.

Even when respondents had reservations about a policy's impact, they felt it was necessary to be engaged with the process as it is important for them to reflect the policy environment in their messaging. In the BP case, respondents indicated how it was necessary to create the understanding of how falls, which formed the focus of the NSF, were related to osteoporosis, which then provided the scope for pharmacological interventions to be introduced into the discussion.

> *We have to work in the environment that we're given, we end up working in such a way that **even if** something like **a national piece of guidance like an NSF we believe is not going to have a huge impact, we can't necessarily afford not to be aware of it,** engaged with it, and try and **ensure that we believe it's moving in the right direction** to make sure that the **access to our treatment is proportionately represented** as one of the elements, and I think another good example in the osteoporosis world is where's the emphasis? Is the emphasis on falls or is the emphasis on osteoporosis treatments? I mean the end goal is to prevent fracture, but you could, depending on how the policy's arisen in the Health Service and I think the **NSF for older people** was very much from that sort of social dynamic, it **went much more the falls route, than the osteoporosis route**. So at a very minimum **we needed to create some understanding and education about how they could interplay** and how they would link together, so that's the sort of role that we would play **to try and connect the dots** to make sure that you got the piece of policy and understanding of that (CS1.2).*

In the PDE5 inhibitor case, it was a case of trying to tie in ED with cardiovascular policy through inclusion in the QOF framework as an early marker for underlying cardiovascular disease, as respondents indicated that this carried a far higher political priority.

> *They started **reviewing the QOF points** beginning of last year and we let the British Society of Sexual Medicine know that they were reviewing the QOF points, and two GPs that specialise in this area, they put together a presentation on the **link between cardiovascular disease and ED**, but their way of approaching it, is that you should be, in your consultation with **men of a certain age, or with certain comorbidities, you should be asking them about their sexual function.** The whole idea is basically, particularly for cardiovascular disease, the arteries in the penis are one of the smaller arteries in the body, so if they're affected, then there's a good chance that at some point in time, your bigger arteries are going to be affected too, so you could **manage that patient's cardiovascular disease very much sooner, if you just asked them about their erection function** and from what I understand that's still in discussion, it's hasn't been resolved (CS3.3).*

The strategy in the statin case focussed on achieving acceptance of lower cholesterol targets within policy (reduction from 5mmol/L (total cholesterol) and 3mmol/L (LDL-cholesterol) to 4mmol/L and 2mmol/L), which respondents indicated was

supported by some guidelines and commensurate with the beliefs of clinicians. At these lowered targets, it would render generic simvastatin, even at its highest dose, unsuitable as it cannot lower cholesterol to that extent alone.

> ***Simvastatin gets about 65% of people to five and three.*** *So it's looking for a 35% market share, or market place you're fighting for between ezetimibe, atorvastatin and Crestor.* ***If the QOF went to four and two, it all of a sudden becomes a 50% marketplace.*** *So overnight you know you've got half the market to go at as opposed to a third of the market, which obviously has a commercial impact (CS4.2).*
>
> ***Economics*** *is what* ***drives guidelines****. Can the* ***population afford four and two cholesterol guideline****? QOF's had a massive impact, the next stage is will QOF go to four and two? (CS4.2).*

Utilising guidelines to change focus of message/deflect drug-specific issues

An analysis of respondent views indicated that the importance of guideline messages can shift in accordance with events that occur during the drug lifecycle. While a lack of differentiation in the AA guidance was initially perceived as inconsequential for some of the drugs in that class, the guidance took on a new significance when some were later associated with adverse reactions. Highlighting evidence that the emerging side effects were also a potential feature of the disease provided justification to include surveillance of physical health within national guidelines in disease management. In doing so, the result was to deflect the emphasis from being that of a single drug issue to one of a class issue (disease-induced as opposed to drug-induced).

> *A good example is the* ***whole physical health associated with patients with severe mental illness****, it's very poor, there's a* ***lot of education needed*** *and psychiatrists are not used to dealing with anything other than the mind. But* ***these patients are at more risk of getting diabetes they have poor diet, they don't exercise, they tend to be overweight****, there's lots of things they need to manage, they tend to smoke, they tend to drink a lot, so you've got to really* ***look holistically at how you manage the patient*** *and we* ***put a lot of money into trying to educate people on that****, trying to make sure there's guidelines, we did* ***a lot of work with NICE, lobbying*** *NICE to say* ***physical health is a priority*** *(CS2.2).*
>
> ***We take them [weight gain side effects] very seriously*** *because I think they're serious issues and I think again it goes back to the body of evidence, you* ***look at the body of evidence and what does it tell you*** *and it tells you that* ***there are issues with all atypical antipsychotics****, so therefore* ***that's why physical health is a very important debate*** *for us and something we take very, very seriously (CS2.2).*

Providing the means of implementing policy objectives

Respondents perceived their role as being central to how the recommendations from policy or guidelines are implemented. They leverage the objectives of policy to justify the use of their products in helping to achieve them.

> ***What's the environment like, what are the key priorities in the UK, are there government policies and pressures that we can leverage from the communication perspective that says you should...this is really important to you because the government are asking you to do this and our product will help you do that?*** *(CS2.2).*

The messages have to be communicated effectively through the correct channels, otherwise the impact is limited. Industry representatives can act as the conduits through which the information is conveyed, or alternatively respondents indicated how they sometimes provide the financial resources to communicate the recommendations to as wide an audience as possible, providing the message is conducive to their product or the disease area.

> *It's a* ***double edged sword****.* ***If we had very, very close relationships with those guidelines and the development of them, the guidelines would lose a lot of credibility*** *that we need them to have as the Industry. So we have to take a* ***very much arms-length view*** *of those guidelines. What we have to do is through the activities that we do,* ***through the scientific education****, we hope at least that* ***we're laying out our stall as to how we see the world, how we see what's important,*** *how we see the factors that are critical, and those are taken in with the same view that other companies are putting out around their products and the view that the clinicians themselves are developing and sharing, but* ***when it actually comes to the production of those guidelines, no, we don't get any significant input.*** *What we do often, is to make sure that* ***once they have decided what they want to do****, who they want it to go to, what they want to say,* ***we can get involved in the how*** *(CS1.1).*
>
> *In the* ***classical Royal College thinking, 'I produce the guidelines and the fact that I've done it is now enough'****. The fact that no one knows where they are, or what they say, or* ***no one's aware of them****, and no one's doing anything with them, used to be irrelevant. I mean 'I've done it, it's there'. So I think where the Industry does work, I wouldn't say collaboratively but they're all working in the same direction is that* ***we're all interested in making sure that once they've (guidelines) been done they get a wide dissemination in audience****, and that's where we would, for example, support, you know,* ***if things cost money to reproduce and reprint, or to distribute, they could be done from sales representatives, we would do that****. But we would be* ***very ill-advised to get very close to the shaping of them****, because that would then, in all likelihood, backfire. Because you would* ***end up with something that people didn't believe in or didn't trust*** *(CS1.1).*

Accepting and adapting to the imposed limitations of policy

Sometimes the policy response of the NHS has forced the Industry to change strategic direction. In the case of generic simvastatin, the cost implications for the NHS were such that original messages became untenable.

> *The **drive for simvastatin by the NHS** probably has **been quite unprecedented**. Statins are such a high focus class, the NHS chose to kind of prioritise these as an **area to save money**. It was **chronic, and five million patients treated.** The **NHS** demonstrated that it was a bit **more sophisticated than perhaps what it used to be in terms of exerting its will on prescribers** and that's a model that's likely to apply to the big markets going forward I think so they've now seen what they can do whereas they weren't sophisticated enough to be able to do that in the past (CS4.3).*
>
> *Shortly after the launch, simvastatin went generic and at that point you have to have a look at things and say okay, our **activities need to be credible**, so is it appropriate to be asking for new patients as the first-line patients to be on rosuvastatin? Well probably not. The price of simvastatin, it actually took a while for the price of simvastatin to fall, but soon or perhaps it was probably a**bout a year after simvastatin went generic the NHS kind of really started to gear up behind generic simvastatin**, **it was the right thing to do**, the price dropped to £4 a month on simvastatin 40 at that time and therefore that kind of **prompted a strategy change** to say look, we need to think carefully about the kind of patients that we're asking for. So doing the right thing for the NHS and also being seen to be credible as well. So at that point, our marketing was very much around **use simvastatin first, and if that doesn't get your patient to target then rosuvastatin is the right statin to use second-line** (CS4.2).*
>
> *I think it took a little **while for us to kind of get to grips with the extent of the NHS drive behind simvastatin and what that actually meant**. It was quite unprecedented, the scale of it, it, internally it took a little while for everyone to kind of really sit up and understand it if you like and **work through the implications** (CS4.3).*

In response to this restricted prescribing environment, interview data described how the branded statins now target high risk patients that require more potent drugs than maximum dose simvastatin to get them to cholesterol targets. It is a fraction of the original market, which has had a significant impact on their diffusion. While accepting of the NHS argument, respondents did raise concerns that incentivised switching policies implemented by the NHS were being imposed at the expense of clinical need in some circumstances.

Individual prescribers started to change a bit, but ***PCOs[21] got hold of this****; we can treat four or five patients with simvastatin for the price that we can treat one with atorvastatin, and we started to see* ***restricted prescribing policies and actually over and above that, active switch policies, getting people off low dose Lipitor and on to high dose simvastatin*** *and there was actually* ***financial incentives put in places by some PCOs****, so we were in I think an* ***unprecedented situation*** *of PCOs literally paying the GPs in some parts of the country to get people off our drug …now let's be objective about it, you could see why they would do that, you've got pressure on healthcare costs, you had the* ***NHS in a period of financial crisis through 2006, you could see why they would do that****. The concern that we had was that…the policies that had been put in place were sometimes quite blunt, literally get people off Lipitor and get them onto simvastatin and while* ***a clinical case could be made for people being transferred from 10mg of atorvastatin to 40mg of simvastatin****, that* ***wasn't always interpreted that precisely****, so we did see* ***patients being switched off higher doses of Lipitor*** *and those patients probably* ***needed to be on those higher doses*** *because they were giving a magnitude of cholesterol lowering that* ***couldn't be achieved with simvastatin****, so we were very concerned about that, so higher dose Lipitor; atorvastatin, is continuing to grow because it's more effective than those statins that are available generically, but we've seen quite a decline in the 10 and 20mg doses as a result of switching across to the generics (CS4.1).*

[21] Primary Care Organisation (later became Primary Care Trusts or PCTs).

5. ADOPTER ATTITUDE

'Attitude' was a theme that encompassed the breadth of social philosophies held by either clinicians or patients identified by nearly all respondents as either enhancing or hindering the diffusion of an innovation (more usually the latter). This theme has manifested itself in three very different ways in the cases studied through the:

- characteristics of professional groups;
- altered perception of certain diseases;
- risk mitigation behaviours of non-specialists.

5.1. Clinician conservatism

The slow rate of technology adoption in the UK is well reported and has been linked with the conservative attitude of clinicians in the UK maintaining the *status quo*. Respondents viewed conservatism as an ingrained philosophy of the risk-adverse clinical culture in the UK, but views were polarised as to its impact on diffusion. Some believed that this conservatism delayed the use of new drugs, whilst others thought it displayed valued clinical judgement. In the PDE5 inhibitor case, the notion that conservatism can benefit the first entrant in a class was raised by respondents. The first in class generally has the challenge of overcoming the *status quo*, but in some ways it has far more points of differentiation on which to change attitudes than subsequent entries within the same class once the first has been widely adopted, even if they offer genuine relative advantage.

Staying with what they're used to and status quo is one of the biggest barriers to diffusion *(G1.2).*

If you've got a ***technology that offers a benefit****,* ***as long as you believe that the eventual peak of your curve where adoption rests and stops is the right level, then does it matter that it's quick or does it matter that it's slow****? I mean if it's quick you should actually be* ***getting the best benefit for the most people more quickly****. I think the problem that* ***people worry about is that it overshoots,*** *and it goes to somewhere that it shouldn't be, and then they have to bring it down again. But if I look at most disease areas and I look at what we spend,* ***take statins for example, however fast they've been adopted, I think we'd say we're still way off target from the number of people that could benefit versus where we are*** *(CS1.2).*

Conservatism is not a bad thing if you believe that quick adoption gives you unnecessary risk*, or a quick adoption leads you to adopt a category more than you should be doing normally. So I think some people could argue, if you say* ***look across the Atlantic at the US you might say that they may be taking a little bit of risk too early because it really depends on what's driving adoption*** *and there are arguments in the system that say there* ***may be some structural things that they have that might drive it too quickly****. And you might say it drives it too high so that* ***you lose some of the things that we would prize in the UK, clinical judgement, and personal relationship****. But I would say on the whole even things like* ***evidence-based medicine is striking a blow at individual freedom for physicians*** *to do exactly what they wanted, and* ***I'm not sure that you've got hugely good healthcare when people do exactly what they wanted****. So I don't think it is a bad thing (CS1.2).*

Medicine uptake tends to be faster in other countries *than it is in the UK.* ***We are inherently more conservative*** *and have more kind of, you know,* ***mechanisms to slow the uptake of new drugs*** *than is the case elsewhere now. I guess sometimes, t****he first product on the market benefits from that when new drugs come in****, but I think basically there is an awareness of Viagra, a trust in it, I mean it's one of the very few pharmaceutical products that has a genuine brand image, you know people talk about Viagra in the way that they talk about Hoover you know, it's become a sort of a genericised trade name. It's the one that people ask for, it's the one that Doctors have been comfortable with and trust and you know, I'm not saying that there's a loyalty to it, but I think* ***it's incumbent on the new entrants to say well what is the advantage of our product over Viagra*** *and you know, I think the honest answer is, there's little advantage, so* ***in the absence of any kind of cost efficacy advantage, they're probably going to get used less*** *(CS3.1).*

Some respondents perceived conservatism as part of the British cultural identity, but others were mindful that there are other factors within the health system that encourage this attitude, such as the publicly funded nature of the NHS and its structural hierarchies. Interview data alluded to the reliance on the judgements of recognised authorities, be that opinion leaders within the field (see Theme 8: Key opinion leaders), or from guidance bodies, such as NICE before a new technology is adopted by the majority of prescribers.

Different in other countries. The ***rate of adoption in other countries is incredibly quick****, which by itself tells you that* ***other people are trying it for themselves****, they won't necessarily…and that* ***they [UK clinicians] need somebody in authority, or a recognised authority to tell them that it's good. Risk management and so on*** *(G1.1).*

*If you look at the **UK** specifically there is a challenge there because **we're the slowest adopting country probably in the globe**, but at least in the Western world **we have the most structural barriers, with conservatism built into the system in terms of how slow it is to adopt new technologies** (CS1.1).*

***Physicians want to find a way of taking indirect trial**, **because direct trial with their own patients is in its own right is quite risky**, because they're actually giving patients things that change their health state, so they want to be confident through indirect trial **through clinical trials, colleagues experience, endorsement by their senior people, guidelines that they are actually mitigating a lot of their risk when they choose to use that product** (CS1.1).*

***If on the NHS something doesn't work the patient will come back and you can give him something else**. **If in Germany that doesn't work the patient might change their doctor**, so the **doctor has a motivation to give the best possible treatment**, whereas I don't think that's quite the same. And **as a nation we're more conservative in our trial of new things, we're more 'let's wait and see'** whereas, I mean you find some markets where they're …particularly **Japan, the uptake of new drugs is fantastically quick, they're more innovative**, and I think **that's a character thing** actually (G1.1).*

Some respondents perceived conservatism as being an embodiment of clinicians' need for experiential evidence (see Theme 2: Clinician/patient experience). The degree of comfort associated with products that have been on the market for several years and accrued safety and effectiveness data was perceived as preventing rapid switching to new products. The notion was that it takes time for clinicians to build up the level of experience required to tip the balance of changing their practice.

***For some clinicians, five years on the market is not enough for them**. **They would always choose something that's been on the market longer.** I guess **Atorva's been on the market for 11 years now, and therefore they're more comfortable with that** (CS4.3).*

*I mean they're quite conservative, you know, well **all physicians are quite conservative as a group** so they don't - **particularly in the UK - they don't rapidly try new drugs**, you know, **they're quite cautious and they will try anything in a couple of patients** and then **build up some gradual clinical experience**, **so they didn't switch overnight by any means**, you know, they gradually built up their experience with Risperdal and gradually **over the last sort of fourteen years they've been switching patients to atypicals**, and I think **most psychiatrists now will - although not payers** - most psychiatrists **accept that there are marked benefits of the atypicals over the older drugs** (CS2.1).*

While these mechanisms serve to absolve risk from the decision making process for an individual clinician, respondents did indicate that delays resulting from this conservatism may act as a disincentive for new drug development.

I don't think always being very slow to take up new drugs is particularly beneficial for patients. To think that ***some of them don't become widely used until 20 years after, when they've gone off patent****,* ***(a) that doesn't particularly benefit those patients, and (b) it doesn't reward the pharma company that invested all that money in developing it.*** *I'm not saying necessarily you should put all your patients onto a brand new drug in the first year, but I do think it's a bit sad that we're very slow to adopt new medicines in the UK (G1.2).*

In addition to the conservative attitudes of adopters towards the uptake of new drugs, this attitude may also extend to the companies involved (also see Theme 9: Company cultural heritage/perception). There was a view from some interviewees that negative perceptions of the Industry from some groups within the NHS did present a potential barrier to adoption of new drugs. While respondents felt they are working towards the same aim as the health service, they were often regarded by some to have an entirely opposite agenda.

What I find quite interesting is the ***level of hostility towards the industry from****…not from doctors but from* ***the paying side****. Really interesting. I've been to a number of conferences where* ***I was made to wear different coloured badges, even though I was a delegate and not a sponsor, where people said to me things like 'oh you're the enemy' and I'm thinking it's really interesting, because actually we're not.*** *We clearly represent some difficulties, but we actually find the solutions.* ***If we didn't provide the drugs we wouldn't be able to treat patients****, so, I find it really interesting that there is quite* ***a level of hostility back towards the industry, that the industry does not feel towards the NHS payers. Certainly not towards the clinicians*** *and so on (G1.1).*

5.2. Disease Perception

The failure of clinicians, patients or the wider society to recognise the significance of a particular condition was cited by respondents as a barrier to adoption. In the BP case, the view that osteoporosis was traditionally considered a feature of ageing slowed diffusion. Respondents felt these perceptions are often formed through a lack of knowledge or understanding about the condition and continue to persist until specific treatments become available that provide a basis on which to address the issue. Indifference is further intensified by paternalistic attitudes in conditions that

become prevalent with age, particularly if comorbidities discourage a position of active intervention by clinicians.

They knew about bone thinning, bone loss, I mean it may not have had the established criteria of defining the disease, but the condition was there and the ***symptoms were very much acknowledged because even dowager's hump was…has been there eternally, it's just that people didn't give it a particular name or understand exactly how you defined the disease*** *that was behind it. I think they were actually as* ***dismissive*** *as 'this is just a natural part of getting old. Hey* ***it's not really a condition it's just something that happens when you get older****' (CS1.1).*

I think ***they didn't really necessarily understand the extent of the problem****, because some of it is almost they say* ***'well this is part of getting old'****. And two, I don't think* ***people actually appreciated and really understood the whole process of osteoporosis*** *and what it actually meant and* ***what was physically happening****. Because it was much more of a dominance in older women, I think it's a bit like the menopause,* ***there was an element of trivialisation of the disease****, and perhaps not taking it as seriously (G1.2).*

Because they're elderly they've got other concomitant conditions which take priority*, so they come in* ***not complaining about osteoporosis*** *they come in complaining about back pain, they're coming in with depression, they come in they're hypertensive, they've got hypercholesterolemia, you know,* ***they've got GI problems, and as soon as you say 'you've got GI problems at 70…oh you'll never take something like this, caustic, so not going to even bother, I'll give you calcium instead' and just hope that that's good enough.*** *So, you know, they do tend to treat on a holistic basis (CS1.3).*

Embarrassment on the part of clinicians about discussing certain conditions was also seen as a barrier by respondents as it can result in failure to explore alternative treatment options or provision of advice that can aid patient compliance.

I think ***our market share reflects our expectations now, I don't think it reflected our expectations at launch,*** *and I don't think our expectations at launch were unreasonable, but what we find is that* ***there's…hugely latent prescribing around Viagra.*** *Some patients will come in and* ***they will just ask for it, and the GP, embarrassed to have a conversation that goes into any depth says yes okay, and writes the prescription for it, without suggesting that they might know better****, so there's quite a lot of that goes on…it's a cultural icon (CS3.3).*

The other thing that we have an issue with is all of the ***information you need to take these treatments effectively, GPs weren't necessarily giving to patients****. I mean we did some* ***research last year which showed that nearly half of all consultations, the patient gets the FP10 and that's it, no advice, no leaflets****; all three companies do product leaflets that help the patient get the most out of their treatment, take it appropriately, leave the right amount of time, you know, not put too many expectations on themselves or their partners,* ***really good advice; they weren't being given out for half the cases****,* ***all due to embarrassment*** *(CS3.3).*

I know ***NICE put some guidelines on diabetes education*** *which is when we sort of focused on it here, but actually what people were doing was* ***taking the sexual function or erectile function question off their template locally*** *on the computer system rather than ask it,* ***or skipping over it rather than asking it…embarrassment on their part*** *(CS3.3).*

Similarly, the embarrassment faced by men with erectile dysfunction and the trivialisation and stigmatisation of the disease prevented potential patients presenting for treatment.

> *There were some groups that **criticised the medicalisation of what is a very normal part of getting old,** you know and the shift from the use of terms like impotence to erectile dysfunction was associated with that. I would still to this day completely disagree with that, I mean **this is a real medical condition and it needed to be seen and treated as such**. It needed the correct terminology applied to it, but you know, there still **remain people that don't take the condition seriously and say it's just part of ill health and getting old; well it isn't** (CS3.1).*
>
> *The stats are like 40% of men over 40, 50% of men over 50, 60% over 60. So you've got absolutely loads of men out there [with erectile dysfunction]. But of those, **only one in ten come forward.** So when you whittle it right down you're only ever treating a very small population at any one time. If you think that two thirds of these men are dropping off at any one time as well, you've got men coming in...as many men coming into the system as there are going out. Market growth really for these drugs is only around about 10%. **You still have a massive amount of patients out there, because they don't come forward, because a) men don't particularly pay any attention to their health, which is terrible, and b) this is just embarrassing, this is really very, very personal to talk about** (CS3.2).*

5.3. Non-Specialist Risk Mitigation

The vast majority of drugs are initiated within secondary care by specialists, but then managed in the community though primary care services once a patient's condition has stabilised. For some conditions such as schizophrenia and osteoporosis, interview data implied there is sometimes a resistance to this transition. Lack of confidence amongst non-specialist doctors to manage certain conditions was seen by respondents as being the reason for reducing the number of potential prescribers, which presents a barrier to widespread diffusion. In this case, patients would be referred, perhaps unnecessarily, to specialist secondary care services to mitigate any perceived risk for the generalist.

> *The other factor is **there aren't five osteoporotic patients coming in and asking for osteoporosis treatment every day into the doctor's surgery**. It's not like pain or GI problems where they've [GPs] got people in every minute. **If they see one a month it's a lot, so it's relatively low down in their mind set**. And this isn't a criticism of them, it's an observation, you know, this is the way it is, it is just another **disease which is very low down in their priority list, they don't really feel confident about treating them** (CS1.3).*

Whilst there's an interface with primary and secondary care, primary care do not like dealing with severely mentally ill patients*. Even today where PCTs are holding the budget etc. this is a group* ***of patients that they do see that the specialists need to own and manage*** *(CS2.2).*

GPs are not confident in prescribing atypicals *for the indications that they are licensed for. They might use them outside for other things, but the average jobbing GP is not going to be comfortable prescribing for schizophrenia, and we found that when they do make changes,* ***they will phone the psychiatrists up or they will do something else, so they won't make initiations*** *(CS2.3).*

Industry views suggested that the perception of how serious the consequences of a disease are also affects the relative priority afforded by prescribers on treating certain conditions. In this sense, risk mitigation can force chronic conditions that raise predominantly quality of life issues down the list of priorities when compared with those with fatal consequences.

Then of course ***there is a spectre of litigation if you're not treating****, which does factor into the doctor's psyche.* ***Never going to appear with the treatment of this [osteoporosis]****. You know, they're not going to say…I mean it should have done, because 'that fracture, that hip fracture is preventable if you had treated this, you know doctor' but* ***they don't have that same worry factor as they do with a heart attack. There are different grades of worry shall we say*** *(CS1.3).*

5.4. Industry Response to Attitude Barriers

<u>– Counteract conservatism by aiding decision making</u>

With the belief that conservatism is an innate professional characteristic, respondents discussed how they are limited in what they can do to change their behaviour, but by aiding the decision making process through education and awareness, they can accelerate uptake rates. By shifting the diffusion curve further to the left, the aim is to engage the early/late majority, who are responsible for the exponential increase in growth at a much earlier stage in the lifecycle before competitors have an opportunity to become established in a field.

We're not necessarily trying to change the eventual diffusion curve*, because I think I'm a great believer that your product is as good as your product is, and it fits into the disease area as well as it does.* ***What you can do though, is you can accelerate how quickly it's adopted*** *(CS1.1).*

*We try to make sure that the **general barriers that people have to adoption**, and they're pretty common, it's like I need to **know that there's an option** that I need to make. I need to be thinking about making a decision, **decide that I actually want to do something**, **evaluate my options**, which will sort of start with gathering data, and then **critically appraise them**. And so **that's what I think we do**, **we can accelerate, and I think successful marketing in the pharmaceutical world accelerates the decision making process that people would normally have so it allows you to have your early adopter to move faster, you're moving the majority more faste**r, and if you **can halve the time that they take to make their decisions you can speed up the adoption** (CS1.1).*

– Counteracting disease perception by obtaining disease recognition

According to respondents, altering disease perceptions can be a significant driver in diffusion of a drug. Disease awareness campaigns (also discussed further in Theme 7: Market development; subtheme 7.2: Raising disease awareness) serve to counteract negative attitudes and perceptions held by patients and clinicians towards certain conditions that are otherwise not readily discussed, whether as a result of social stigma as with mental health disorders, or attitudes of apathy towards conditions of ageing as with osteoporosis, or as with erectile dysfunction, that was subject to both. To achieve that change, it may require that a collection of symptoms is formally recognised and acknowledged as a 'disease state'. Respondents suggested that this may only happen once understanding has reached the point where it becomes possible to clearly define the condition, and there is a tangible means of prevention and/or treatment, as in the BP case.

***Everybody expects old ladies to look like coat hangers, it's just 'ah you're getting old'** you know. I mean you look at the **elderly triangle sign on the Department of Transport and they've got dowager humps** haven't they?! I mean they use the Department of Transport to say you've got osteoporosis. You know, it's a natural state. **Well it isn't a natural state,** and it is **actually treatable, and you've got to break that sort of mindset and acceptance. And you can only do that with the power of communication** (CS1.3).*

*Did we create the disease, could be a criticism that we often face, not in this case, I mean **osteoporosis just hadn't had any suitable treatment** apart from calcium you see. **Everybody knew osteoporosis needed, bone health needed to be treated, but we treated it in diet and exercise** and undoubtedly diet and exercise do have an effect on bone health, and of course we'd all understood and accepted that there was a degeneration of female bone health, particularly after the menopause, but we had nothing to do, **we couldn't treat it, so it was accepted.** It was just sort of one of those things, it's growing old. And **today we don't have to accept it** and that's great. You know, **it's no longer a fatal disease, it's a chronic disease** (CS1.3).*

For the PDE5 inhibitors, respondents believed that by adopting the scientific terminology for impotence of 'male erectile dysfunction' it helped to change attitudes towards the condition to one of a distressing, but treatable disease rather than a lifestyle problem. Respondents felt however, that the impact of this change in terminology resonated more with clinicians than patients.

Impotence doesn't somehow sound as serious as erectile dysfunction *and we wanted it to be serious, because* ***for many people it is serious****…you wouldn't need to sample too many men's opinions on what they value most in their lives, to actually find out that they value their sex life very, very highly. I mean this is intuitive to us, but you know,* ***we could foresee people just dismissing impotence, so evolving it to erectile dysfunction was part of that. Erectile dysfunction is just a better scientific term as well, people sort of associate impotence with a lack of libido*** *(CS3.1).*

If you look at the number of ***searches on the Internet of erectile dysfunction versus impotence, Joe Public is still putting in impotence*** *a lot. I think* ***medicalising the term has had more of an impact on physicians to take the issue seriously*** *(CS3.2).*

Impotence has become a slightly pejorative term*...you describe somebody who is impotent, you are not necessarily commenting on their kind of you know, sexual abilities, I mean* ***it's a sort of character thing almost really,*** *so it needed to be a* ***more precise term that was about the medical condition with less baggage attached to it****… we needed to get good messages out about* ***what erectile dysfunction meant to people,*** *the* ***fact that it was a distressing medical condition****, which it is,* ***people's lives and relationships are suffering dreadfully as a result of what is a treatable medical condition;*** *one question is whether we overplayed that, but I think it was* ***important to be quite…austere about it in order to kind of make the point****. I mean, there was* ***a danger, particularly with the level of media involvement, that it all did become a bit of a smutty joke*** *(CS3.1).*

– De-stigmatisation

The so called 'medicalisation' of a condition was seen as an important facilitator of diffusion where embarrassment is a barrier. In the case of erectile dysfunction (ED), the challenge for Industry was that disease perception was intertwined with the social construction of masculinity. They needed to dissociate these two concepts, and by focusing on the tangible medical causes of ED such as diabetes and cardiovascular disease, respondents described how ED became a symptom, much the same as hypertension, of a wider vascular disease.

***Men with ED take about 18 months on average before they'll seek treatment**. In addition to that, **their erectile dysfunction, if it's caused by an organic cause, ironically it tends to be intermittent**, so if it's caused by diabetes, one time they'll be able to get an erection and the next time they won't, the time after that they will, then they will, then they won't; it gets gradually worse and worse until it's almost complete ED and they can't get it any time they try, and you have **interwoven in that, some performance anxiety, because each time they're attempting they're thinking, well the last time it didn't work, so will it work this time** and it kind of puts them off a bit, and it's…**integral to their definition of them as a man**. All the research that we've done with men with ED, says when they get erection problems, they don't feel whole or complete and they don't feel like they're fulfilling their role within their relationship, but they **don't want to bother GPs about it because they think that it's just a sexual thing and not a medical thing**. So one of the things that, I think all three companies have tried to do and we've really tried to do particularly, is to say, **it's a medical thing that causes this** (CS3.3).*

***Many men don't know that their ED is probably, or can be caused by coronary heart disease, by their diabetes.** They don't know that it's because of the other comorbid conditions that they've got. So I think **there's a huge amount of work to be done with the public on that and for them to understand that it's not, you know, it's actually not their fault** (CS3.2).*

***Even if ED is included on the QOF, it's going to be a hell of a hurdle to overcome people's embarrassment about asking that question**. Some of it comes from people feeling that **it's personal or it's an invasive question to ask**, but some of the ways we've seen it done really nicely is, particularly with patients with diabetes is to say well '**it's quite common for patients with diabetes to go on and have problems with their erections, is this something that you might have witnessed yourself** you know, with your erections?'...I've seen people do that with patients and that really helps, because it kind of, **it's not blaming them and it's just saying, this might happen, and even if they say no it hasn't happened yet, it's planted that thought in their mind then that they can then come back and say well I am having erection problems, obviously because of my diabetes** (CS3.3).*

6. COMMUNICATING RELATIVE AVANTAGE

Relative advantage is the extent to which an innovation is perceived as being better than its predecessor(s). Analysis of respondents' views indicated that while clinical need ultimately determines the value of an innovation's relative advantage, a key determinant in successful diffusion is firstly ensuring that a drug's relative advantage is sufficiently differentiated from its competitors, and secondly that these features are clearly communicated to adopters. All respondents raised issues about the communication of relative advantage, predominantly because they conceptualised this as their role. Furthermore, as a drug only has one opportunity in its lifecycle to establish the concept of relative advantage, poor initial perceptions of prescribers can be hard to overcome (see Theme 2: Clinician/patient experience).

6.1. Differentiating Relative Advantage

Early communication of relative advantage was seen as critical by respondents, with a clear view that tangible benefits were a necessity for clinician acceptance of such advantages.

> *I think first and foremost* ***it's a fantastic product****. You* ***don't get an uptake curve like that if it doesn't deliver what we say it will do****. If something doesn't work and* ***doesn't work in the right way people aren't going to use it irrespective of any input from the company behind it****. Nor would we expect them to (CS2.2).*
>
> ***The debate about marketing, is it better to have a good drug marketed badly or vice versa is over, you've got to have the drug*** *(CS4.1).*
>
> *What we do is* ***we help people to understand the benefits of drugs, but ultimately what makes them successful is are they good drugs or not****, and* ***Viagra*** *is a very good drug, it* ***does exactly what it says it does and it does it very well, consistently, and repeatedly****. It's a lot* ***easier to market and sell a very good drug*** *that works and one that's got such a distinctive profile as well (CS3.1).*

Most respondents indicated those innovations that do not offer a sufficiently large enough step change in relative advantage tend to struggle, contrary to the perception

often portrayed by Industry critics that good marketing alone can make a success of a poor product, or one for which a clinical need does not exist.

*If you have just gone from using **typical antipsychotics** which are **perceived as being** you know, **fairly unpleasant** for patients to take, and **go into Risperdal (risperidone) or olanzapine**, you'd **have a step change in how well these drugs are tolerated**, so the **fact that Seroquel (quetiapine) is better than they are, you probably don't kind of notice** as much (CS2.3).*

*The graph tells the story; it's **not captured the imagination of prescribers** because I think, it **had even less differentiation from Viagra** to be honest. **Lilly had a proposition to put forward on the basis of longer half life**…it **was a point of differentiation**; there's really **very little meaningful differentiation for vardenafil** (CS3.2).*

***First movers generally maintain an advantage over their lifecycle over subsequent entrants unless one of those entrants does bring to the table genuine differential advantages**. And I think **Zyprexa (olanzapine)** entering after risperidone but having **genuine advantages** is a good example of that. And based on what we've seen **quetiapine,** also a good drug, but arguably **didn't offer anything more** than Zyprexa (olanzapine) (CS2.2).*

Analysis of interview data suggested that an element of compromise between a drug's characteristics may be required to translate to relative advantage, rather than it being a case of a new drug having to be consistently better than its predecessor in all respects. In the AA case study for example, later entrants to a market where relative advantage had been defined by improved side effects had to balance increased tolerability against reduced efficacy to prove relative advantage.

*Really **the market sort of falls into two categories** I would say, well, for the atypicals, **Risperdal (risperidone) and olanzapine** which are viewed as having **good efficacy but having some side effects**, so with olanzapine it's weight gain, Risperdal it tends to be EPS (extrapyramidal symptoms) or prolactin, and then you've got the **newer drugs like aripiprazole and quetiapine** that are seen as being **very well tolerated but not seen has having the same efficacy** as Risperdal and olanzapine (CS2.1).*

In contrast to some consumer products however, respondents did highlight how pharmaceuticals within the same class do at least offer more significant differentiating features with which to appeal to adopters.

*Looking at its relative benefits versus its competitors, and obviously **in pharmaceuticals** compared with other industries you're actually lucky because there is probably **a lot more in terms of differentiation between brands in the same market**. For instance there are **a lot more differentiators***

***between one atypical and another than two different cans of baked beans**, so you would be looking at basically **what attributes doctors find most important**, so we do some market research around that and then also look at and **then compare that with what actually our attributes are**, and something like you can identify which are the key attributes you are going to promote to customers (CS2.3).*

Diffusion of innovations theory states that innovations that are simple to understand and use will prevail in the marketplace. This was borne out by both the AA and BP cases where less complex dosage regimes, in terms of single as opposed to titrated doses and regular weekly doses compared with cyclical regimes, were thought to have facilitated eventual market leadership.

A unique issue that affects the diffusion of pharmaceuticals is the typically large cost reduction that occurs with the arrival of generics which can diminish the impact of established points of differentiation. Several respondents believed that clinician and patient preference may remain for drugs that offer ease of use as their differentiator, but prescribing policies favouring generic formulations may reinstate older more complex drugs driven by cost savings. Simvastatin, once superseded by more potent drugs with lower costs and side effects (atorvastatin and rosuvastatin), came back into favour once it went off patent. The progression of time and accumulation of clinical experience with a drug however, can reduce complexities surrounding a drug, such as the removing the need for titration with some of the earlier statins. Competitors were forced to adopt new strategies to differentiate in order to retain some market share.

*We try and get that message across to physicians saying well, they've got to take a drug so **why not take a drug that's low dose, gives you the same benefit as something that could be higher dose and obviously you tend to get more side effects as you go up the dose range in any drug**…When there's no generic simvastatin on the market it was a lot easier because you're basically saying **10mg as opposed to 40mg gets you the same end point, which is easier and less expensive** (CS4.2).*

*I think there's a realisation that you need to be yet more aggressive with high risk patients and I think Lipitor is still gaining growth and more usage through the use of higher doses in really seriously high risk patients who need really quite aggressive therapy. With the **genericisation of simvastatin and some of the changes to pricing** that have happened, it has **become extraordinarily cheap** and people*

have been prepared to say, I'm ***not going to worry so much about sort of starting doses****, I'm going* ***to use the highest licensed dose of simvastatin to treat the majority of my standard patients*** *if you like, because it's just* ***so cheap to do so*** *(CS4.1).*

What that is really, is an ***amalgamation of continued growth in the higher doses and a drop off in the use of the low doses, so there's quite a bit of dynamics sitting behind that flat line*** *(CS4.1).*

6.1.1. Real versus perceived benefits

Analysis of responses indicated how Industry is reliant on clinical evidence to demonstrate relative advantage, but clinicians may inform their own reality about relative advantage through their own experience, or that of their colleagues (see Theme 2: Clinician/patient experience). This opens up the possibility for misconceptions of relative advantage based on perceived rather than actual benefits.

Atorvastatin is a very, very good drug. People are very comfortable with it. You've just ***got to show there's an advantage****…it's like anything isn't it? You've* ***got to make people move from their comfort zone and the only reason they'll move is because they believe in something****. So you've just got to try and make them believe that yours is better than X, Y, Z that they're using currently. Our policy is to try and* ***present as much evidence as possible*** *(CS4.2).*

The ***doctor has been told the Seroquel (quetiapine) works****, but we know they are* ***not so much clinical evidence-based but own experience****.* ***They use Seroquel, they use it at too lower dose****,* ***it doesn't work as well as olanzapine, it doesn't work as well as Risperdal (risperidone), so they then have kind of negative perceptions****, so yeah, it doesn't have very many side effects, so they really buy into that, but* ***end up reserving it in a kind of second or third line position*** *(CS2.3).*

Perceptions, according to respondents, can be influenced by many factors, both logical and illogical. Interview data suggests that perception as opposed to reality can be both beneficial and harmful to a drug's diffusion. If a drug is perceived to be better than it actually is the positive effect is obvious on diffusion, but conversely, perceptions of reduced capability acquired through inappropriate use can be damaging to continued diffusion.

Doctors' perceptions are very different from reality *across any market you look at, and so it's like, if you have* ***got a situation where this drug is actually a lot more capable than what the doctor thinks it is, how do we change that****?* ***Do we change the way we work? Do we change where we position it?*** *(CS2.3).*

*I've sat in market research where **GPs have seen blinded product profiles and they have not liked Viagra**. You **unblind that product profile and suddenly they rush to justify their Viagra prescribing**, because that's what they've been doing but, you can't take it with food, it takes an hour to work, it finishes within four hours you know, **both Cialis and Levitra are advances** in terms of convenience for the patient and efficacy, **but they still stick with what they know best** (CS3.3).*

*They have obviously done more **research** there in terms of **looking at what the perceived attributes of the product are versus its real attributes**, because let's face it, **if it was just about clinical trials there wouldn't be a single drug company that had a big sales force** (CS2.3).*

Respondents indicated that they may only have a short period of time to convey relative advantage before the commercial opportunity is lost. In the BP case, risedronate offered tolerability advantages over alendronate, but the company was unable to capitalise on this feature before a weekly formulation of alendronate made daily BPs effectively obsolete.

*Quite honestly they stole the march on us on that. As I say it [risedronate daily] is a **genuine product innovation**, but I think we **underestimated the grumbling amount of discontent about daily products**. I think we genuinely **underestimated how much of a difference that would make** and it [alendronate once weekly] just came at the right time where there was a lot of things coming together at once and it usually is that sort of crescendo effect of more than one activity coming together at once that gives them that little bit of a tipping point (CS1.2).*

Monitoring and correcting misperceptions early in the lifecycle was thought to be important. The PDE5 inhibitor case highlighted this, as a few respondents indicated the importance of education in correcting beliefs that the drugs could be misused; a factor that was potentially jeopardising uptake. This case also illustrated how perceptions about these drugs were influenced by the skilful use of language to imply benefits without actually stating them.

*I think a very important thing is, **it was a difficult drug to abuse**, in an area where **if there had been abuse of it, it would have been very difficult to manage**, so you know, you **had to be sexually stimulated for it to work**. If you **took it in overdose**, you know, to be really frank you didn't get a better erection, you didn't get better at sex, you didn't have longer sex, it was just, it **only did what it was meant to do**…it's a **normalising drug as opposed to an enhancing drug**…**even today, there are people that still assume that Viagra has an aphrodisiac effect** or is you know, somehow it's going to you know, boost the libido which it absolutely doesn't (CS3.1).*

***One of their big commercial successes** has been the way...**what they say versus the way it's been interpreted**. So **if you ask health care professionals which of the three PDE5s gives you the hardest erection**, okay, **they'll probably say Viagra**. **Viagra have never said they give a harder erection**.*

They say they give a hard erection. They say it that much though, that it gets this thing of 'harder' *(CS3.2).*

6.1.2. Market entry position

Analysis of the interview data found that the extent to which companies have to differentiate themselves from their competitors depends, in part, on their market entry position. The first drug in a class to reach the market assumes leadership, but first entrants can be displaced by second entrants providing differentiation messages are successful. Subsequent entrants may find this harder, but not impossible, providing they offer relative advantage genuinely valued by clinicians. Atorvastatin for example, was fourth to market and rosuvastatin, which came after had an impressive initial uptake attributed to its greater potency that offered a means of easily meeting policy objectives of the QOF, before safety concerns and generics prevailed (see Theme 2: Clinician/patient experience; subtheme 2.3.2: Safety warnings/concerns).

I know that it [atorvastatin] ***came as close as any drug can come to being abandoned*** *as a project because it was going to be the…I think the* ***fifth to market worldwide*** *and I think the sense was, who wants to be fifth then, and I think it was literally down to one or two scientists keeping the belief alive that led to Warner-Lambert choosing to reinvigorate its development and then bring it to market because they* ***believed that it had genuine differentiation***. ***We weren't at the forefront of a race to get a new technology, we were debating whether or not our technology was differentiated enough to be worth launching*** *(CS4.1).*

I think ***all other things being equal you'd want to be first in class***. *But* ***if you're second to market and you're not too far behind the first drug and you've got a good argument then that might be a better place to be but rosuvastatin has certainly suffered significantly as a result of being sixth to market***. ***The impact of the genericisation of the market has been kind of immense****...I mean the curve looks quite substantial and looks highly successful but it is a 4% market share after being on the market for five years, so it's not the most fantastic of uptakes.* ***This initial phase was considered to be a really good launch. This early phase was above AstraZeneca's expectations and kind of widely regarded as being a really strong launch*** *(CS4.3).*

Respondents indicated that whilst being first to market offers obvious and lucrative benefits, it can also be risky. There was a belief from some respondents that arriving in an immature market with low priority and lack of disease management consensus often involves considerable market development resources (see Theme 7: Market

development). Ultimately the first is paving the way for subsequent entrants who then face fewer barriers and less cost. This does not necessarily only apply to the first introduction of the molecule, but also being the first to introduce a new formulation if that requires a change in adopter behavior.

The one that came first wasn't the one that won the market, the one that came second did, and I think generally there's a ***big advantage to being first and second, but maybe coming second, so somebody else had done all the hard graft*** *(CS2.3).*

It's not the most competitive field by any means; it's quite a niche field is this. Risedronate came yes, and it did look very similar and they tried to get to emulate the evidence suite. It's ***always difficult to second entrant because your customer is going to be asking for 'well are you better than the one that I use today?'*** *(CS1.3).*

There are ***some disadvantages****, because* ***if you're first in class you've got to sort of carve out that part of the market****, to give you an example with Risperdal Consta we're the first atypical long-acting injection, so we've had to really sort of create the benefits of that.* ***But*** *I think normally if you look at products that are* ***first in class****, they* ***normally do quite well,*** *I mean* ***sometimes second in class can****, you know,* ***not be a bad position either because you can learn from first in class and the market isn't saturated****, and for example olanzapine did quite well as being second in class, Risperdal oral was the first atypical but actually olanzapine came in second and did well. I think it's* ***harder if you're then coming in third, fourth, fifth in class*** *in the market, but I think first and second, you know, you* ***can still come in second and do very well and sometimes overtake the first in class*** *(CS2.1).*

In a way it was great entering a market heavily dominated by one company because they'd done a lot of the pre-work for you*. I guess you could...you could view it in a couple of different ways. You* ***could view it as the market's absolutely happy and satisfied and everybody knows about that one,*** *so that's really, you know, really difficult. Or you could* ***view and say well the taboos of ED, some of the barriers have come down, men expect and have the idea and notion that a tablet would actually work for them.*** *You know, so t****hey're used to that concept****. But you do obviously have challenges of getting over a big brand (CS3.2).*

While the consensus view was that the position of first entrant is associated with many benefits, other respondents highlighted how first entrants also face the prospect that if the majority of the 10-12 years of remaining patent life following approval is substantially consumed by building the market, there is limited time to recoup investment before the market becomes generic. If the market is established, or even partially established at the time the second entrant is launched, then its remaining patent life can be far more profitable than that of the first in class, providing it can demonstrate intra-class relative advantage. This can prove more challenging than the first entrant's task of inter-class differentiation.

*You've got to **look at the lifecycle of drug development** really and say where do certain events come into play? Typically from molecule patenting, registering the molecule which then gives us sort of 20 years of commercial life, but in the **first 10 years** of that typically that is just **governed by regulatory trials, and safety and efficacy trials**. So you're really just trying to find what's the right dose? Does it work and is it safe? And so you're identifying the population in which it will be efficacious in. And **that will give you your licence**. **So typically we've only got 10 years of marketing of the drug when it is actually available for use** within whatever population (CS1.3).*

In compensation, Industry views suggested that first entrants do benefit from a level of interest that later entrants may not have, and usually a period of exclusivity from class competition, allowing time to secure uptake by as many adopters as possible. If clinicians have established experience with one brand, switching is less likely to occur when competitors enter the field.

***Viagra** had this sort of **window of several years if you like in which it was the most effective, the most convenient method** (CS3.1).*

*I think it's **harder to be first to market because you tend to do a lot of the market preparation for other products**. **Unless you've got something absolutely unique that no one can touch for ten years and then you can reap the rewards**, but with this market in particular, **the market preparation was done by simvastatin to a large degree or pravastatin. They'd sold the fact that lower is better** and so on (CS4.2).*

Formal cost effectiveness analysis is an increasingly important factor in diffusion and respondents had conflicting views on how market entry position could have an impact on assessment. While first entrants typically had accrued a greater evidence base at the time of assessment to substantiate claims, proving cost effectiveness can sometimes be an easier prospect for the second entrant compared with the first in circumstances where there is no standard of care.

*If you're **first in class** you may have to **invest quite a lot more in education, than if you're second in class** or **sort of its well-established how to treat that condition** already. We would traditionally say **first in class will get the highest market share traditionally**, but the situation now is that **with NICE** particularly where you've got your cost benefit**, if you are first in class you may end up comparing yourself versus nothing, because with quite a lot of conditions standard of care is nothing**. So to produce a cost effectiveness against that **can sort of be quite challenging**. So actually it's much **easier sometimes to be second in class and compare your cost benefit, versus the first in class**. So actually I think one of the consequences of NICE is it discriminates against innovation. **We would never not try to be first in class** (G1.1).*

Statins are the single biggest class of drugs in terms of NHS spend *by some margin, even with simvastatin generic and kind of cheap as chips, it's by far the most costly if you like in terms of what the NHS, what the NHS pays out. So at local level you're always going to have* ***drugs and therapeutics committees creating local guidelines, formularies and what are you going to choose?*** *They want to choose a* ***drug that's got best evidence and that's the one that's first to market because it's done the studies*** *(CS4.3).*

6.1.3. Perception of brand identity

Analysis of views amongst respondents suggested that associating a strong brand identity with a drug, even in a market where direct to consumer advertising is prohibited, is another means of differentiating relative advantage. While branding in a pharmaceutical market appeared less essential as with consumer goods, interview responses suggested that a brand embodies both relative advantages and company values that can influence prescribers' and patients' perceptions of the product and the manufacturer. This provides an additional point of difference in crowded markets where opportunities to differentiate on a drug's characteristics alone diminish for later entrants.

If you've got a problem with erectile dysfunction*, you're* ***going to want Viagra****, you know you are going to feel a little bit fobbed off,* ***you want the most well known one you know, not because of any kind of desire to be fashionable or anything, but just because you tend to trust the established brands*** *you know, so that's* ***why you buy Hoover, that's why you use Biros****; the originator brand will tend to do well…interesting in pharmaceuticals, It's not always the case…but I think that's probably because there is* ***less branding in pharmaceuticals****, so you know,* ***Tagamet will get overtaken by Losec, because there's no loyalty****, because what's Tagamet, what's Losec, nobody really knows, but with Viagra…* ***there is a trust and an understanding of the first brand*** *(CS3.1).*

Perception of brand identity however, can become just as much a barrier to diffusion if it does not resonate with adopters' values. Respondents indicated how the iconography associated with a brand image, while appealing to some, can ostracise others. The perception of one brand may also impact on others if efforts to differentiate relative advantage are not communicated effectively.

When you think of that brand, it conjures a very hard image in your mind*…I think there is still some of that that we have to get over. I mean one of the things that we had at the time was the* ***media played on people's perceptions of what Viagra did,*** *but at the same time* ***they then just said well 'and this is going to be for 36 hours'. So you are going to be a Viagra person but for 36 hours. If you have safety concerns you are going to have those concerns, but over 36 hours*** *(CS3.2).*

They did market it [sildenafil] quite aggressively. *If you look at worldwide* ***imagery for Cialis you'll always find a couple in it. You'll never find a man particularly alone*** *in it and so you* ***build up a brand identity which is...it is for couples****, it's for, you know, for people to bring their love life back and therefore* ***it's not aggressive in that sense*** *(CS3.2).*

6.2. Conveying Relative Advantage

Even if relative advantage is clearly differentiated, the manner in which this information is communicated can impact upon diffusion. Respondents discussed how effective communication firstly relies on creating awareness of a new product's relative advantage in those most likely to adopt. Awareness stimulates interest, but it is the detail offered by drug representatives that translates the importance of those relative advantages to clinical practice. Communicating a drug's relative advantage is just one component of marketing.

Immediately [post-launch] it's around awareness*, it's just around trying to make physicians aware of obviously the launch and aware of* ***the key data, and aware of the benefits****. Then I guess as you go on, you perhaps* ***need to be more sophisticated once you've made them aware****. Obviously some of them, you* ***present your initial argument if you like and that's going to work for some people****, but then you need to think about* ***for those physicians who are not using the product what are the kind of arguments*** *that are going to be necessary for them to* ***give them the comfort to use the product****? So that might be things like the* ***cost effectiveness or the long-term safety, those kind of things****. So* ***you'd try and make as many physicians as possible aware and aware of the key data and then look to be more sophisticated based on your uptake thereafter*** *(CS4.3).*

I've very high faith in the ***professional ability of the enormous majority of physicians to make a good decision*** *about which drugs they're going to use and* ***sales and marketing in this industry*** *for me is about just* ***making sure that people have access to the information to make those decisions*** *(CS4.1).*

6.2.1. Simplicity/clarity of message

Message clarity relating to relative advantage and correct use appeared critical for successful diffusion. Complex or inconsistent messages that lack a clear point of focus create confusion that can impact on clinician and patient experience and was cited on several occasions by respondents as being a cause of suboptimal diffusion

for drugs in the AA, BP and PDE5 inhibitor classes (see Theme 2: Clinician/patient experience). To avoid some of these issues, respondents indicated that advisory boards composed of key health professionals in the field are used for honing messages.

> ***We run advisory boards*** *as well, which - the purpose of them is not to raise awareness, it's* ***to gauge feedback from customers on for example the clinical data or the proposed messaging*** *(CS2.1).*
>
> *One of the world opinion leaders has said to me, one of the things he likes about our drug is that* ***it succeeded almost in spite of its marketing, instead of because of it****.* ***Some of the clinical trials were designed with too low a dose****.* ***It was a real confused picture over what dose should a customer use****, what is the best dose, whereas, with the statins say,* ***with simvastatin****, it very clearly says where the evidence is,* ***10mg works but 20mg is the dose you should use****,* ***it's very clear; in this case there was never a clear dose message*** *(CS2.3).*
>
> *When you actually look at...and there's a* ***clinical paper talking about PDE5s*** *published in the European Journal of Urology, it says okay* ***a lot of people fail****, but are they truly failures because the companies say that* ***these drugs work at 70% to 80% efficacy rates, so why are they failing****? And all they did was* ***re-educate them****, gave them enough dose...enough dose of six to eight tablets to be able to actually try the medication properly and* ***put them on a high enough dose that they...you give them the best chance of success****. And they found that* ***of those failures, about three quarters of them, actually it worked perfectly fine for them****.* ***It's just that they hadn't been told, with Viagra for instance, you can't take it on a full stomach*** *etc. etc. and you need to plan that. It's simple things like* ***GPs forgetting to tell men that...or men not hearing****, because we're not exactly the best listeners, men not hearing* ***that they need sexual stimulation to get an erection still****. So they literally take their tablet, wait and an hour and nothing happened. So I've...it obviously doesn't work for me (CS3.2).*

For another of the PDE5 inhibitors, respondents from that case believed the complex and changing messaging that lacked a strong differentiating focus failed to secure that drug's intended position in the treatment pathway.

> ***You give them [clinicians] a really good differentiator*** *for your product and* ***a reason to believe that that's an important differentiator****, which is what I think, we've done really* ***in the last year, and we're really focused on the differentiator, but leading up to now, we've changed our messaging an awful lot*** *as well, so … I think has* ***added some confusion in the GP's mind****,* ***so if you said to them, what does Levitra stand for****,* ***if you asked 100 GPs you would probably get about 30 different answers, whereas if you ask them what Cialis stood for, with them, it would be 'it's long-acting; and it works for the whole weekend'*** *and it's really those phrases we've come across because, from pre-launch, all the way through to now, their main message is, they last 36 hours (CS3.3).*
>
> ***They promoted a couple of papers saying they [Levitra] would work for patients who had failed on Viagra.*** *They* ***said that they would work in men who were...who'd suffered with diabetes****. And they also came with a message which was* ***we're very potent****.* ***From a physician's point of view, I've just heard you're working in my difficult to treat patients because you're potent****. I'll use you there.* ***So I have a diabetic man who suffers with ED who's failed on Viagra…how often do those men walk through my door? Hardly ever*** *(CS3.2).*

In the BP case, the necessity to explain complex dosing regimes to patients, or a journal's requirement that explanation of unexpected trial outcomes be included in publications, all contributed to losing the cleanliness of the messages about the drugs in this class. Similarly, reactive communication following a safety warning in the statin case deviated away from the core message. The resulting confusion amongst clinicians was perceived by respondents as having compromised the drug's rate of market recovery.

I think we do make mistakes and I think we probably, as a company, we ***maybe jumped a step in terms of dose ranging so we have an issue*** *in the sense that, it's not a problem from a clinical point of view, but I have an issue* ***from a trial point of view that our 2.5 milligram arm disappeared out of the trials*** *and so that's not good because* ***you have to explain it****, so we should maybe have dealt with that in a different way. So* ***instead of one nice clean crisp message we ended up with sort of 'well I have to explain a few things about my trial before I can now give you my clean crisp message' so it's not so clean and it's not so crisp*** *(CS1.2).*

Keep to core messages*.* ***Don't, you know, flip around all the time from loads of different messages****. Because* ***during that first dynamic early phase the message was, you know, low dose to target once a day****. And* ***then we had Dear Doctor letters it was all over the place for a bit*** *to be honest,* ***there wasn't clear messages****, so I think having clear messages is the key to what you want (CS4.2).*

6.2.1.1. Tailoring the message to adopter needs

Clarity of message can be enhanced by tailoring the communication materials to the meet the needs of the different adopter groups in diffusion. Respondents believed each adopter group wants something different from the communication materials, which is in accordance with Rogers' adopter categories i.e. innovators want early evidence, while late adopters are more likely to be influenced by peer-pressure.

The ***innovators and the early adopters might have actually quite low usage but they drive a huge amount of influence to drive acceptance of these as established treatments for the people that follow****, so you usually only start to see the pickup when you've got the early adopters and you're into the early majority that's when you see the take up. So they tend to follow those curves so I think* ***each bit of material has a role to play in how you educate those different groups, because they want to hear something different*** *(CS1.1).*

For your ***innovators clearly they're looking for things like the evidence****. Actually your* ***laggards will probably be peer pressure*** *(G1.1).*

There's a population of ***GPs and specialists out there who are interested in this...your innovators****. And for those people they're* ***always going to be on the cusp of getting things very, very early*** *and you*

*can **point them in the direction of a clinical paper, the evidence can come through and it stays with them, because they're interested**. That's probably 1%. The **only time when a GP would come across this is when a representative pretty much brings it to them**, or their PCT was to say something to them or...It has to be something of that magnitude. **It's not just a paper being published** (CS3.2).*

*By the time you've got a **peer review publication, or you've got a full systematic review or meta-analysis**, it's a little **bit too late to be taking that information to the people that are your innovators and early adopters**. Those are **wonderful tools that can actually help address the concerns of the middle majority** (CS1.1).*

Messaging can also change over the lifecycle of a drug to accommodate the needs of the different adopter groups who are the prominent prescribers at particular stages. In the BP case, one respondent described how early promotion focussed on the science of the treatment to appeal to the evidence-driven innovators. During later stages as the properties of the drug had been established, the message softened to focus on more emotive factors

*The advertising campaigns, they give an image of how you're projecting…in this one we **started off with a sort of bionic woman image,** you know, it all **focused round the skeleton and the strength of the skeleton. And it became much more emotional here [later stages of lifecycle] about grandmothers that could be active with their grandchildren and that kind of thing** (CS1.3).*

*We just dealt with it **by not necessarily having a one size fits all approach**, so **talking to GPs in one way, talking to nurses in another way, talking to consultants in another way, and making sure that what we were saying resonated with them** and supporting them where possible in either promoting their clinics or, maintaining their clinics (CS3.3).*

6.2.1.2. Targeting the message

Respondents described how clarity could be enhanced by targeting messages towards specific groups of adopters through disease-specific journals for advertisements or focussing representative activity on demographically receptive areas. Messages therefore, have to resonate with the intended audience for it to have an impact. In the PDE5 inhibitor case, some respondents described how the decision to focus on diabetes-related erectile dysfunction alienated many prescribers.

If you are in osteoporosis surely you want to deal with the people who treat osteoporosis, so ***you would be very targeted*** *to a particular…I mean therefore the* ***trade magazines which they read for instance. If it's a GP product then you would go to Pulse, GP****, that kind of thing (CS1.3).*

The impact of the representative is important and who they go to see is important, and we can determine a number of ways for a drugs launch. We can do this by sort of listing of ***GPs as a target list*** *and say to them 'these are the* ***ones that are most likely to adopt the drug because they treat a lot of patients like this'*** *so* ***osteoporosis is a very non-homogenous distribution of disease****, it tends to be in the* ***elderly*** *and it tends to be* ***treated in the socio-economically active area****…so you tend to find that there's* ***certain geographies where there's a great deal of use, and there's certain geographies where it's just got much more transient, a young population, no point in going there,*** *that's just waste. So you will find that, and* ***you'll find surrogates for how to identify those GPs*** *and off you go and see if you can see them and tell them the story. And that's part of the diffusion. And there's quite a lot of skills involved in doing that (CS1.3).*

We went from a very broad market to only looking at patients with diabetes, *so then the* ***GPs were saying, well I'm not the GP who runs the diabetes clinic, therefore this isn't resonating with me****, so we had* ***our messaging and our targeting of GPs weren't perfectly matched,*** *and so we* ***went back out to a broader messaging****, because we were targeting a broader group of doctors to make sure that if they weren't interested in diabetes and they weren't managing patients with diabetes, we still* ***had something of interest to say to them*** *(CS3.3).*

6.2.2. Product awareness (advertising)

Awareness was conceptualised by respondents as the knowledge that something exists. The general consensus amongst respondents was that while advertising increases awareness of a new product, whether this then translates to increased prescriptions is uncertain due to a lack of an effective tangible measure of its impact on prescribing decisions.

Then of course there's ***advertising. Difficult to prove the value of it****. You can* ***only measure really the inputs on that. You can't really measure the outputs****. I can't do a sort of return on investment calculation on advertising, because you can only really measure awareness by market research, so I can go and advertise something, and I come and talk to you and say 'can you remember an ad for this osteoporosis product?', 'yes'. Okay 'can you tell me the name of it?, no'. 'Maybe it began with an 'F'?', 'ah, Fosamax (alendronate)', right so you're getting a prompt rather than spontaneous, and from that you can get message diffusion.* ***Do you get use of the drug because of that? Possibly not, but what you are getting is an awareness that the drug exists and so when you get any representative calling, that recognition is triggered 'ah yes, I'm aware of that, that's for osteoporosis****'. Right, okay, now* ***I can engage with you about that subject****, so it's sort of a necessary part of the mix (CS1.3).*

It would not be unreasonable to suggest that awareness drives demand for an innovation, but respondents indicated that unlike other markets, a greater depth of information is needed by a clinician as part of their decision making process than

what can be delivered by advertisements. In this sense advertising merely serves as the hook on which Industry representatives can then engage with clinicians on the detailed arguments that are the key to influencing prescribing behaviour. Most respondents indicated that advertising is therefore limited to raising awareness around launch, or when there is something new to highlight about a drug such as a change to formulation to increase interest, rather than as a continuous reminder throughout the drug lifecycle. It was seen as a useful tool in crowded markets such as the statins where there is a need to concisely highlight points of differentiation, but its impact diminishes over time as other factors become more important in influencing prescribing decisions.

Advertising is great at launch to raise awareness *…but in my experience, very,* ***very rarely, does it actually initiate a prescription. Doctors need to know an awful lot more about your product before they'll consider initiating a prescription*** *(CS3.3).*

Seroquel is 10 years old, Seroquel is ***not the newest drug in the class****, they know the drugs. You know when we have done market research****, psychiatrists, 100% of them are aware of Seroquel, so why advertise****, you* ***only want to advertise if you do something new*** *(CS2.3).*

Advertising generally is a tool. It's used only to generate awareness of a brand. It's designed to stimulate an individual up to the point of trying a drug after which personal experience takes over *(CS2.4).*

I would put ***advertising****…in this market [osteoporosis],* ***very low down in priority****. It's not a widely…you know, your* ***awareness is more important to come from a diffusion out of secondary care*** *experience of the drug, help in identifying the right patient …I mean if you go into* ***statins, advertising will be a bigger****, you know, it's a noisy,* ***noisy market****, people are pounded with messages they* ***need a strong image of what is their choice****. That was less important in this field. (CS1.3).*

The suggestion from one respondent was that a drug could diffuse independently of advertising providing the environmental conditions are right, such as in the AA case where the level of pre-market excitement was such that it compensated for any potential limitations in the advertising campaign.

*With hindsight **one of the things I'm less proud of now was the initial advertising campaign** which we used at launch. But that also gives me… you know, it gives me **reassurance that it really was the quality of the medicine which led to the uptake and not any of the sales and marketing effort** put behind it. I just don't think it was very impactful… it sort of went against what conventional wisdom would now teach us as a good advertising campaign…it **didn't really differentiate our drug, you know, from other drugs within the class** (CS2.4).*

There was a perception amongst some respondents that messages conveyed in the form of advertising are often viewed sceptically due to the overt association with the company. A degree of disassociation between the manufacturer and the message about the product is therefore necessary in the health sector in order for it to carry any credibility. Arguments conveyed by key opinion leaders are therefore seen as being stronger with regards to influencing behaviour (see Theme 8: Key opinion leaders), with advertising providing a channel for reiterating relative advantage.

***Advertising does work**, I mean people are responsive, but it depends on what grounds you're selling that advertising. It's **easy to say that in an ideal world advertising should be the reminder and not the argument**. And I think there are **much better tools suited to be the argument**, and that's usually **ones where there is a high degree of trust as to the person presenting the argument**. Quite rightly there's **natural scepticism if the drug company says something** you know, indeed the manufacture of anything, I mean it's like there's a real healthy scepticism whereas if **it's said by other people where there's a higher degree of trust you're more likely to believe it**, but then **sometimes you still need the reminder** to actually 'yes, I remember that' (CS1.1).*

In direct contrast to the view that credibility comes with dissociation from the product, other respondents expressed frustration that the Industry is unable to communicate directly with patients. In the PDE5 inhibitor case, respondents felt that information was not always accurately communicated to patients by clinicians as a result of embarrassment that either affected the patient's perception of the drugs or limited the choice of options available (see Theme 5: Adopter attitude; subtheme 5.2: Disease perception).

*The one thing I would like to see and I feel that would be kind of righting a wrong, is the ability of companies to be able to communicate sensibly and factually about the prescription medicines that they make available. I think, **as a member of the public, taking a medicine, you should have the***

right to hear from the manufacturer, what they see the benefits and risks of that medicine being and our inability to communicate with patients is a problem *I think. What I'm not necessarily advocating is the US style , broadcast media approach. I think the* ***one thing that we would like to see in Europe is the ability to communicate directly, factually and responsibly with patients about the medicines that they take*** *(CS4.1).*

6.2.2.1. Managing Expectations

By raising awareness, there is a risk that the developing interest in a product can result in raised expectations of the drug's abilities. Respondents indicated the importance of managing expectations, especially for eagerly awaited new drugs, such as the AAs. Most respondents expressed the view that exaggerated claims about a drugs performance will be quickly exposed and that it is important for successful diffusion that performance meets expectations. Interviewees made reference to the practice of 'underpromising and overdelivering' as a tool to manage expectations.

Very few people were sceptical when they first came across the drug because of the lengths we had gone to not to overpromise and therefore underdeliver*. People went into their first few half dozen trial patients with realistic expectations and therefore there was a* ***greater chance of exceeding those expectations*** *which in itself* ***leads to more repeat usage*** *of the drug (CS2.4).*

Respondents disputed the fact that Industry only ever reported positive evidence, arguing that once clinical experience became out of step with Industry messages, the opportunity for further use was severely compromised.

There was ***conditioning of people internally****. You know, to be fair to physicians and fair to their patients,* ***do not, when this drug becomes available, position it as a panacea****, as a … you know, as a cure all in the area of mental illnesses/schizophrenia because it is not. I mean* ***only refer to the data which we have, only refer to the results that we have,*** *it's not a perfect medication and* ***people need to understand the true objective profile of this drug, you know, the good bits and the bad bits*** *(CS2.4).*

We were strictly told at the time was 'Here are some preference studies. This is where it's at'. But also ***'here are the study limitations and here are the things that every single time that you sit in front of a physician that you must point these things out and then let them...then discuss it'*** *and see whether this actually does or does not reflect what they've seen in their own clinical practice (CS3.2).*

We were very, ***very careful not to overpromise and to be very conservative in the claims and the positioning for Zyprexa (olanzapine) at that time. So as not to damage expectation and damage the chances of Zyprexa being used in populations where it should be needed.*** *I mean the landscape in*

general, not just within schizophrenia is ***littered with examples of where drugs have been launched which promised the earth but deliver inevitably substantially less****. And so we were at pains to train the sales force and to* ***tailor our marketing materials*** *to really almost* ***undersell the drug****. Because I think there was such excitement at the time of the data being presented on the academic circuit pre-launch. People of a more optimistic personality type might be tempted to call olanzapine, clozapine without the side effects. Which, of course, a claim of which cannot be made without head to head data which we didn't have at the time. So we were at great pains to* ***point out the efficacy data which we did have, the side effect data which we did have, but also proactively urge people not to draw too optimistic a conclusion from that until head to head data became available*** *(CS2.4).*

The shape of the diffusion curve immediately post-launch was thought to be a product of the amount of anticipation and awareness generated in the pre-launch period. Respondents believed that the uptake of the AAs was invariably a consequence of the interest amongst clinicians, but the unprecedented media hype surrounding a new treatment for ED in the PDE5 inhibitor case was responsible for fuelling anticipation amongst patients. Respondents indicated how this was a far more difficult situation for them to influence, as they were unable to communicate with patients directly to manage their expectations.

There probably wasn't a ***psychiatrist in the land that wasn't aware of Zyprexa (olanzapine) a year before its launch let alone at launch because of the excitement that had been generated in the academic press*** *and so, you know, arguably one could have pressed* ***ahead with the launch of Zyprexa with no advertising whatsoever other than to let them know it was available*** *(CS2.4).*

There was 100% awareness before launch, in the population…not even just amongst the medical world, I mean, everyone knew about Viagra, I mean, and the pent up demand of course, was phenomenal. *The States caused enormous difficulties in the UK.* ***We were always going to launch in September, October****, subject to the vagaries of the regulation process;* ***the States launched in June*** *and…boy was the cat out of the bag then, I mean* ***that's what led to the press****…this was every radio station, every news station, every newspaper for about six months.* ***We had to manage a very exasperatingly difficult media situation in the UK, because we're not allowed to talk about****, I mean this is the thing that people often don't realise that you know, we cannot…****we can respond to questions, but there's no way we can sort of issue press releases*** *unless it is sort of, I can't remember what the code definition is, but unless it's of very significant public interest (CS3.1).*

6.2.3. Product justification (representative detailing)

Respondents confirmed that interpersonal relationships play a significant role in diffusion. Unlike advertising, respondents indicated that drug representative product justification continues throughout a drug's lifecycle, as face to face exchanges can be

far more effective in persuading an individual to accept a new idea, compared with mass media channels. Product justification needs a more personal approach that offers the opportunity for clinicians to scrutinise the claims being made in a two way exchange of information.

There are very few elements that actually work on their own, because if there was one element that worked entirely on its own we wouldn't do anything else. The one ***in the model that people are finding it very difficult to potentially walk away from is rep selling****. Some have tried it and I think the bottom line is that rep selling* ***does work, it's a personal level, a personal direction*** *(CS1.1).*

If you look at how people take information on and how much time they have *to take information on and I think there's* ***always that role for the person to come and talk to you about the profile of the drug****. Now,* ***whether that is a medic who has experience in the trials, or whether that's a rep going to GP surgeries, it depends on the drug*** *(G1.1).*

Whilst there was agreement that the interpersonal approach was important for continued product justification, respondents disagreed on the mechanisms involved. Some believed it was simply the weight of repeated messaging from a field sales force – so called 'share of voice'. Any means of increasing the scale of this approach through mergers or partnering with other companies, translated into an increased trajectory of the diffusion curve. It not only brings additional financial resource, but also additional skills and experience. In disease awareness terms there is a combined impact of a large number of different companies talking about the same condition, even if the product messages are different.

I think the other difference between these two is that this ***[etidronate] is P&G on its own, and this [risedronate] is in an alliance with Hoechst Marion Roussel****. One of the things that we can't offer as a non-traditional pharma company is the scale of an MSD attack, so partnership is then critical. if you're talking about* ***one sales force or two sales forces promoting a drug it's a huge difference****, so we would always have been a little bit under what MSD was able to do because they were a much bigger pharmaceutical company, and* ***we only really became able to do that when risedronate was launched, because we were in a partnership with a bigger pharmaceutical company*** *(CS1.2).*

I think Pfizer has been very good at being able to have ***high levels of contact with general practice*** *and to* ***get a message out relatively quickly to a large population of people*** *(CS4.1).*

I think the thing that ***partners bring, is a wealth of experience that we don't have****.* ***Partnership gives you different things, but it gives you some money, your speed to market because it can bring additional resources to it****. Every time our partners go through mergers they bring, you know, every company brings something new to the table (CS1.2).*

*I think we **increased investment in the product**, and we've **gradually increased the size of the sales force** that we have behind it (CS2.1).*

*I think the **amount of investment we've put behind these products has been appropriate**, but I guess, unlike some companies, we've been able to because we've had a very successful base and **we've had the funds available to do it, and that in itself is also contributing to the uptake and the development of those adoption curves** that you see (CS4.1).*

In contrast to the size argument, in other cases the impact was perceived to be as a consequence of the trust on which these relationships are based, built over many years, which enables the same impact to be achieved by a smaller number of representatives. It that sense, it becomes not just about the sheer number of interactions, but the quality of those interactions that are of importance in influencing diffusion.

Representatives were perceived as an important conduit for relaying information in amongst an environment of information overload for clinicians. All respondents indicated how representatives account for their biggest spend and tends to be an area where any increases in investment are channelled. The personal element ensures that a message is conveyed about their product in a way they want it to be received, as opposed to relying on the information in a standalone capacity.

*I know that the industry has its critics and so on but I think it's **very insulting to GPs** when people write this stuff to say that **just because a rep comes and visits them, they're going to kind of ignore all those years of scientific training because somebody gave them a post-it note**, **they are going to decide to prescribe their medicine**, I just, I don't believe people operate like that. **What is clear is GPs are bombarded with so much information**, so many magazines, so many publications, so many clinical papers, so much continuing medical education, **that if you don't send representatives in to see them, they'll probably never really come to appreciate your product and take it seriously**…so our **large field forces have given us the ability to have reasonably regular contact to share that information**. I don't think it's given us the ability to sort of brow beat or somehow cajole people into prescribing for us, I mean I don't see that it works like that (CS4.1).*

*I guess we have always tried to match them in terms of the level of marketing. It's not always possible to do, but particularly **in terms of representative capacity to see doctors, we try and stay on a par with the opposition**. Certainly **in this early phase** there was very much the thought process that **your uptake would be related to the amount of representative coverage** that you've got, it's **now far less the case** with some of the tools and things that we talked about, the **market's now much more sophisticated**. But **in these early days whilst if you like there was still much more prescriber freedom, then those kind of activities would undoubtedly impact on your uptake** (CS4.3).*

It's ***our biggest spend*** *from the marketing channel perspective, to* ***keep sales force running and then the materials we give them. So they're always going to factor right up there*** *(CS2.2).*

The success of this model is based on the longevity of the relationship with the clinician and the trust that becomes established, such that information exchanged is viewed with credibility. Respondents expressed the view that clinicians value the knowledge possessed by Industry regarding a drug's technical features, affording them the status of credible educators.

Then of course you've got our most expensive component with marketing which is ***the representative****, the individual, and we you know are an industry which* ***still relies on that for diffusion of the education and the message and the awareness of the drug and how to use it****. And it's still extremely valued by the customers. I mean I know there's a lot of cynicism around this but the doctors do need this.* ***A good representative will provide an awful lot of information for the doctor and give a lot of reassurance on how to use the drug, which patient to use it in, then give the doctor confidence that they know, what to look for*** *(CS1.3).*

Customers, they're well attuned to knowing which new products come on the market place and are hungry for information (CS2.2).

If you take say a ***rheumatologist*** *who we would view as a key* ***physician category in the area of osteoporosis probably spends less than 5% of their time managing this disease*** *versus the rest of their workload.* ***So from everyone else's opinion a very highly skilled specialist versus one of our sales representatives who is spending 100% of their time potentially on osteoporosis****, or a medical adviser, or one of our medical directors again spending 100% of their time on a particular disease area, that* ***the level of knowledge is often quite weighted towards the person who has got that degree of dedication*** *(CS1.1).*

Respondents also believed that this personal contact continued to justify the investment, affording confidence not just in individual drugs, but in the company as a whole.

One crucial event which doesn't really kind of pick up here; I suppose because it's quarterly it's sort of flattens it out a bit, was when we split with GSK, because ***we launched with GSK and then at the beginning of 2005, we split up with GSK and lost their field force resourcing, so we halved our field force resourcing****, but I think* ***within a few months, we were pulling it back up again****. I think representatives can be very good, and that's why I was* ***surprised that there wasn't a bigger dip because a lot of the GSK reps were experienced, they had good relationships with doctors****. Doctors over time had learnt that they could trust that representative, therefore* ***you send them in with a new product, you've already got some trust brought in****, just because it's that person's familiar face. We had* ***contract sales forces working for us on Levitra*** *over the years and I think,* ***because they have a high turnover, we didn't get the level of trust*** *brought into it, and it* ***made the job more difficult for us*** *(CS3.3).*

Good rep selling would tend to be based on trust *in the sense that these are, like any other relationship, I mean the first time …if* ***you've got a brand new rep in the field going to call on a doctor for the first time, it's very unlikely that that rep is going to do anything to that doctor's***

***prescribing habits, but if that person has been calling on him for 10 years**, and they understand that they can actually,…there is a **benefit on both sides of the relationship, then it's much more likely that when they come with something different** there probably and hopefully would be a halo effect that you **don't have to re-establish a trust on every brand that you work on** (CS1.2).*

*Looking back you would say at that point we **acquired a lot of much more specialist medicines** and probably **didn't do enough to retain some of the talent that really knew how to communicate with specialists and had that depth of experience and knowledge with the compounds to continue to communicate well**, and I think we probably **lost some ground for a while** in terms of that (CS4.1).*

6.2.3.1. Competitor 'objection handling'

Respondents indicated that when adoption hinged on ability to precisely differentiate relative advantage (as opposed to factors such as diagnostic barriers etc.), representative contact was the favoured medium. In a detailing situation with a clinician, a representative's awareness of a competitor's profile provides a further opportunity to differentiate the relative advantages of their own drug in response to potential objections raised by adopters. In doing so, it can influence diffusion by either retrieving, or preventing further loss of patients who are prescribed their drug. Interviewees indicated that by researching the literature they could be fairly certain of the likely approach taken by competitors even prior to launch and prepare strategies accordingly.

***If it's around differentiating just on the ground, my product's better than your product, sales force, that's where you throw your money** (CS2.2).*

***You almost act as if I was launching this product,** how would I position it into the marketplace, what does the data say, what can we say and you have to **train your sales force** to handle a new competitor so you go into their profiles and you do **objection handling** with them and **make sure that the data they launch with we know as well so that we can talk about the pros and cons to our customers** (CS2.2).*

*All companies **will publish some data in the phase 2 trial, so you can search that, and you build up, if you like, a competitor profile** of what you think, and of course you always **get taken by surprise sometimes, but hopefully not much** (G1.1).*

The extent of response to competitor activity was described by respondents as often being related to a company's current and future portfolio. In the BP case P&G took

the view that aggressively competing against a new entrant with their existing product was an unnecessary distraction given that their next generation product was imminent. Strategies are also dictated by the proportion of market share a drug has access to. In crowded markets, respondents indicated that there is perhaps a stronger driver to maintain share through counteraction of their competitors' arguments. With fewer entrants in a field, there was the suggestion that objection handling is likely to be less of a priority as respondents were amenable to the view that the market is capable of supporting more than one product.

*If this is your **sole product you may try and out promote the competition** but the **fact that risedronate was coming**… and in fact meant to come earlier, I think we probably tried to stay in lock step, or **we never actually competed** (CS1.2).*

*I think there was definitely **space in the marketplace for more than one product**, and you can tell that by where everything goes eventually, and I still argue that we're not over prescribing, I think **this is a disease area** where I still think that you may be…**you're not even over prescribing in terms of the people that are in the high risk group** (CS1.1).*

7. MARKET DEVELOPMENT

Market development (also referred to as market expansion or market shaping) is the process by which Industry attempts to alter the shape of the diffusion curve by increasing the number of patients eligible for treatment. An analysis of respondents' views indicated that expansion is achieved by entering new segments of the market, converting non-users into users, and/or increasing usage per user (in the pharmaceutical market the user can refer to both the prescriber and the patient depending on the context). The process occurs at all stages of the product lifecycle, preparing for arrival, ensuring initial uptake and assuming various levels of priority as an activity as the company's market share fluctuates.

> *If your **typical drug has an uptake curve** like that, there are **three ways where you can actually try to improve that**. And that uptake curve will depend on its profile and what I mean profile is its efficacy profile versus its competitors, its safety, administration, i.e. dosage and flexibility in how you give it, and costs. And it will have an uptake curve that would normally happen without promotion, so there are things that you can do to affect it. **One is to obviously make the curve happen for a bigger, larger amount of curve**, that is can **you increase the overall usage**. So if you like that would be your **commercial effect**. **The other would be to try and make it happen faster**, and there's all sorts of things that you could potentially do to speed up that. Everything **from investing a lot in medical education so that people understand how to use the drug, particularly if it's a new class, or investing a lot in clinical trials, so you've got a lot of data to prove that it's more efficacious**. And so on and so forth, everything through to PR and all sorts of things that you might do there. And then **the third thing that you can do is to make sure that your curve then goes up again at that point where it would have tailed off, so that might be another indication you go into, it might be another formulation** that you derive or something. So in terms of your marketing strategy I think the question is how do you extend one, two and three? And **of those three, speeding up the rate of adoption has the biggest impact** (G1.1).*

7.1. Market Research

Respondents discussed how market research is an important aspect of market development. A clear view was expressed by respondents of the importance of identifying and understanding the clinical needs and attitudes of patients and clinicians in order to gauge how the attributes of a new product will be perceived and how the messages will resonate with adopters.

We would research a new therapy area *in terms of how large the market was, who were the key competitors, what changes are expected in the marketplace, and then also* ***speak to some customers and find out what their drivers were for using various products*** *in the marketplace. From that we would do* ***more in-depth market research*** *focusing on certain areas, so we might want to* ***find out, you know, from prescribers what are the areas that they feel are still unmet in the marketplace and if a new product was coming in, what areas would they like it to address*** *(CS2.1).*

Once you know what the product profile is, what the product is that you're going to launch, ***we do a lot of work in terms of understanding****, in any particular disease areas,* ***what do the doctors desire****?* ***What are their needs? What are their drivers to prescribing? What are their barriers to prescribing?*** *What are the unmet needs in that disease area? What's really going to turn them on and what's not going to turn them on?* ***How do they respond initially to our clinical profile without any of the whistles and bells on it****. How are they going to respond to that?* ***What are the things that they see as unique or they pick up on?*** *And then it's starting to think about how are you going to dress up that product, and how are you going to communicate the benefits and messages around that product (G1.2).*

We think it through ***in the market planning*** *by looking at* ***what audience do I need to communicate with****? And* ***what message do I need to communicate*** *that audience with in order* ***to encourage their behaviour*** *in the use of a particular medicine for whatever benefit that would have for them and for their patients. So* ***you're always looking at it in terms of benefit for them and their patients****, and I know* ***many people might think that that's cynical, of course we'd say that, but actually, unless it does give them a benefit and it gives the patients a benefit they'll never use it****. You know, that's the same for you and I with any consumer brand. So, it's exactly the same sort of mindset that is applied (CS1.3).*

Through understanding disease issues respondents described how it helps to identify where patients are lost from the patient pathway. In doing so, this enables the expected parameters of the diffusion curve to be estimated reflecting the potential patient population if these barriers can be overcome.

How does the patient flow through that system? Is it very clear, is it complex, where could we intervene and educate? In terms of the channel mix though, that goes back to ***strategically what are you trying to tackle****, so* ***if it's diagnosis you're going to throw all your money at educational programmes and disease awareness and thought leader consensus around guidelines****.* ***If my leakage is*** *further down the patient pathway and it's* ***around which treatment do they get, you focus then on differentiating your product from product X*** *(CS2.2).*

At the start of your planning *you will have done some kind of size of the market in terms of untreated patients.* ***What's the patient population****? And therefore* ***what's the expected penetration of that patient population****? So you* ***know when you've saturated the market and when you haven't*** *(CS1.3).*

Key opinion leaders (KOLs) have an important advisory role at this stage in terms of identifying areas of unmet need and providing feedback on what messages and approaches will resonate most with their peers. Together with other clinicians and payers, respondents indicated how they rely on the input of these advisory boards to

enhance both the quality and clarity of their communication strategies (see Theme 6: Communicating relative advantage; subtheme 6.2.1: Simplicity/clarity of message) and to assist in pharmacoeconomic decisions in advance of launching the product.

It depends on what we're trying to find out and how quickly we're trying to find it out, but ***for a new product you test focus groups or key players, what they think, what they need, the brand, the data and you get them building, you literally use customers to build your messages****. If I showed you this data what you think? If I show you this, what resonates better, why, how would you order this story? We literally use them to build our materials (CS2.2).*

Prior to launch we have advisory boards *and they sign consultancy agreements and* ***have input into the data*** *and the quality of the data and* ***what does this trial say to you*** *and* ***if we were to make this claim with it, how would that go down****, what more do you need to see? (CS2.2).*

Our advisory boards *would be a group of people who would say look at the clinical profile for this drug, pre-launch often, and where do you think it will fit into the pattern of prescribing, and that* ***can be clinical people and it can be payers****. As I say there are a number of payer advisory boards as well, as in,* ***look at the clinical profile for this drug, look at the cost we're thinking of charging, do you think that it will get approved for use by independent bodies****? (G1.1).*

Market research is also used post-launch to assess attitudes and barriers to uptake. Respondents however, indicated their frustration of their dependence on market research, which is due to the confidential nature of prescribing information as it is perceived as an indirect measure that can only ever give them a limited insight.

A marketing team will have a means of ***tracking the product*** *that they can…work out perhaps the* ***reasons why the product's being used and the reasons why the product isn't being used****. So that's kind of a* ***continual process looking at what might further drive uptake*** *(CS4.3).*

In that first six months at the end of that we would be re-evaluating communication*,* ***making sure that the recall was getting across and identifying what the issues were****. Maybe doing more qualitative research to get an initial toe in the water of* ***what they thought about the drug, how they would be using it, if they did use it, what were the issues they faced?*** *Things like that, so we've got an initial sense of what, if there were any problems, what they were (G1.2).*

I suppose one of the key things is you have to have the data and given that we can't get prescriber level data from doctors ***we are always living in the dark about who is using the drug, so that's always a barrier for us, and it's done for good reason****, you know, anonymity, blah, blah, blah, I accept all those arguments, but that's our environment that we have to operate in.* ***So we do have to buy quite a lot of market research to get information about behaviours and understanding of disease and willingness to treat and attitudes*** *and things like that. So that's, because that's again important in the diffusion of the drug,* ***unless people's attitudes are right they're not going to do it****. There's a* ***huge market in data provision****, a huge market,* ***because the Industry's entirely dependent on it****, because I can't come to you and say 'I know you've done this, why?' (CS1.3).*

The AA case highlighted how market research uncovered a barrier to their adoption that was rooted in differing perceptions between Industry and prescribers as to what was defining clinical need. Industry believed improved side effects were the driving factor in prescribing decision, only to find subsequently that this was not the case.

> *Now **when we did the pre-launch research**, we identified that **the thing that differentiated Seroquel** from the other two atypicals, **was on basis of side effects, it's going to work as well but its tolerability is a lot better**…, so this slow increase is probably because we sold on side effects whereas **we now know from our insight that although psychiatrists will say the side effects are really important to them, if you have got patients acutely unwell you know, probably the thing that drives their prescribing is efficacy, so taking efficacy as a given was kind of perhaps a mistake (**CS2.3).*

7.2. Raising Disease Awareness

Disease awareness (DA) aims to increase the number of patients eligible for the treatment of a condition rather than an individual drug. It is not subject to promotional restrictions on timing or audience, as is the case with product awareness (see Theme 6: Communicating relative advantage; subtheme 6.2.2: Product awareness), and helps prepare the market and identifies potential barriers.

> *So **we did a lot of GP education before launch** and we produced you know; **worked with, the necessary kind of authority of clinical bodies to produce guidelines** and that sort of thing, so that people, okay as I say, **we wanted people to be able to use the product for commercial reasons, but also we wanted it to be used in an absolutely robust scientific way** (CS3.1).*
>
> ***If I'm launching a product and my issue is diagnosis**, so they come in but it's quite a hard disease to diagnose, **my strategy prior to launch would be having a lot of education around the disease area and trying to get consensus on how you diagnose it in the UK, guidelines in place** before you go with these products for instance (CS2.2).*

Respondents described how DA, whilst having a prominent role before launch, occurs throughout all stages of the drug's lifecycle. The information was believed to equip patients with the confidence and a legitimate basis on which to approach their clinician to facilitate a dialogue about treatment options. For this reason DA campaigns are also often referred to as 'help-seeking communications' Most

respondents agreed that DA is particularly important in asymptomatic conditions, or to highlight symptoms of serious illness that may be confused with other conditions.

*You've got to get **disease awareness into the population so that not to scare them but to make people aware of what they have**, and the **problem with a disease like osteoporosis it's a silent disease** (CS1.3).*

***Do they [patients] perceive they have a disease, so for diabetic retinopathy for instance they wouldn't perceive they have it because there's no symptoms.** So you've got to **do a lot of work** from the marketing perspective **on education around the importance of getting your eyes checked etc. if you wanted those patients to come into our system**. **And they've got to come into the system if we want products sold**. Do they seek treatment for the disease? **If they seek treatment do they get a diagnosis** for that disease (CS2.2).*

*We had the very famous sort of **disease awareness campaign** where it was the mannequins, **we showed how osteoporosis progressed by using shop window mannequins** you see, and it was a very clever campaign, very eye-catching and again it **gets patients aware and the population it sensitises them** to the condition and **makes them engage in that conversation with the doctor** (CS1.3).*

Typically the burden of awareness activity is borne by the first entrant with those following benefitting from the work (see Theme 6: Communicating relative advantage; subtheme 6.1.2: Market entry position, in relation to how market entry position affects extent of product differentiation required). For conditions that are in the initial stages of disease classification, diagnosis and management, respondents believed DA has a pivotal role to promote the major bodies of evidence to counteract any controversial views that could be detrimental to uptake, and to reach a consensus view on treatment.

***The cholesterol lowering market in the mid 90's was unbelievably different than today**. I think it was 1992 that there was an **editorial in the BMJ entitled 'Time for a Moratorium on Cholesterol Lowering Drugs';** There was all of this **debate about whether actually lowering cholesterol was a good thing or not, and we had these amazing extrapolations of findings from some of the early studies that patients taking cholesterol lowering drugs might suffer more violent deaths and, suicides and this sort of thing** and all kinds of theories were being put forward for why that might be the case. Flying in the face of the major kind of bodies of evidence that said look, if you've got high cholesterol, you die of heart disease, if you've got low cholesterol, you don't and we can demonstrate from intervention studies that actually changing somebody's cholesterol level has an impact on survival, so **it was a market in a very embryonic stage with a lot of controversy associated with it,** so you see very modest growth **despite having a major impact on cholesterol levels** and **it just had very slow uptake because the medical community were not really convinced, and certainly general practitioners weren't, of the value of prescribing these drugs** (CS4.1).*

*By 1992 we still don't have a lot of sales there, but **by the time we actually get to a launch we're years into this, and we've got so much experience and so many connections and relationships that***

have been developed, *that I think that was really the work and the conditioning,* ***but you can actually say this is against an environment where people didn't really understand this was a condition****, they didn't understand what limits they should put around the condition to ensure that you weren't going to get over-prescribing or use in people that you didn't need,* ***they didn't understand how to use the products****. So I think* ***a lot of the work that we did in the Didronel [etidronate] days was really linked to actually educating the whole area*** *and trying to get people to focus on this (CS1.1).*

I think that ***a lot of disease awareness work had been done****,* ***Atorva had been on the market for six years by then. Simva had been on the market since '89****, so there would have been a lot of disease awareness.* ***There was good awareness of cholesterol lowering*** *so you know I think* ***most of the disease awareness had been done*** *(CS4.3).*

DA was conceptualised by respondents as something slightly different and softer than the 'education' that takes place between representatives and prescribers in product awareness activities (see Theme 6: Communicating relative advantage; subtheme 6.2.3: Product justification). Communicating information about diseases was described as increasing and enhancing adopters' existing knowledge. This subtle difference dilutes the perceived influence of Industry on the process making it appear a far more passive acquisition of knowledge. By doing so, it is a far more conducive way of engaging health professionals who are the Industry's major conduit through which to relay information to patients, which is essential to ensure the success of a DA campaign.

At the start there was relatively low understanding of this condition*, relatively low experience of dealing with it; I think* ***we worked hard and I think, did a good job to, I don't want to say educate, but to supply information that those that were interested you know, took on board and then shared with patients****, and I think that has grown over time and you know, practice nurses got very involved with a lot of educational work with nurses and so on, so I think in the main, you would say, you know,* ***compared to ten years ago now****, if a patient presents to primary care services,* ***you will get good advice, a receptive environment and good counselling alongside any medicine that's treated, but it was a different situation at the start*** *(CS3.1).*

You need to engage the healthcare professionals to help you with it [disease awareness*], you can't; you know, we've all* ***tried doing it on our own with websites and leaflets and things, and unless the healthcare profession are brought it, they are not necessarily going to hand them out*** *(CS3.3).*

7.2.1. Patient group role

Respondents described how patient groups can provide a conduit through which to communicate information regarding a condition or a class of drugs independent from

Industry. In the absence of direct to consumer advertising in the UK (prohibited by law), respondents highlighted how relevant patients can be targeted with educational material that may stimulate a dialogue with their clinician that leads to treatment initiation. The restrictions placed on brand endorsement through this route, whilst signifying credibility, was thought by most respondents as limiting patient group impact to a class rather than a drug effect.

One of the things we did do, was working with the Sexual Dysfunction Association *and helping to advertise, because they would* ***provide information on local clinics****,* ***so if somebody had gone to their GP and their GP had said to them, at your age you shouldn't be having sex…****which was quite common, therefore****, go away and don't darken my door with your erection problems again, and the man could ring up and they would say okay, well in your area we have these sympathetic GPs who run clinics*** *or these urologists who run clinics and you can go and seek treatment from them (CS3.3).*

There are moves to try and encourage patients to have more of a say in their medication and patients to be told about the different side effects of the drugs, so that they can make a decision. We would support that *and* ***we try and support people like the National Institute of Mental Health who are driving that****, you know, because we think it's right as well. We believe patients should also be given a choice between taking a tablet every day or an injection once a fortnight and, you know, some people would prefer an injection once a fortnight and not have to worry about it, some would prefer to take a tablet every day, so* ***we believe it's important that patients discuss that****,* ***but the evidence is that that doesn't happen as much as it probably should*** *(CS2.1).*

I think ***they're [patient groups] effective in educating,*** *but I don't think they affect sales or curves.* ***They raise awareness of the high cholesterol which helps the statin group as a whole. I don't think it will have affected the rosuvastatin curve****. Anyone who goes to the GP and asks for a statin is going to get simvastatin 40. They're not going to get rosuvastatin 10 (CS4.2).*

7.2.2. Public figure/celebrity endorsement

The use of celebrity endorsement is another way respondents explained promotion could be disassociated from companies to raise the profile of a disease, especially if the individual's personality is sufficiently renowned. The choice, however, has to be carefully considered, with respondents suggesting that figures who were affected by the condition themselves were seen as the most credible spokespeople.

For a couple of years ***we used [a sports celebrity] as a spokesman for our disease awareness campaign because he had ED as a result of having his prostate removed, and it was very important for us that we had somebody whose erection problems were caused by a medical cause. He talked about it in a very mechanical way****, you know, if I had a car and there was something wrong with the engine, I'd take it in to get it fixed, and as far as I'm concerned there is something mechanically wrong, so I've gone to the Doctor to get it fixed…We saw more GPs getting involved as well. I think patients felt a bit more empowered…****I think people seeing him saying that thought well, you know what, if he can say it, and he can go and get it sorted, then I can** *(CS3.3).*

[Another sports celebrity] ***didn't do any good*** *for men with erection problems because he stood up there and said* ***"well if I had it, I would go and go and get it treated"****, and actually* ***what they want to hear is someone going, "I've got it and it's not that bad, and it can be treated, and it's not you, it's not because you are less of a man, it's a thing that happens when you have diabetes or when you have your prostate removed". I think the medicalisation of it needed to have some celebrity endorsement*** *(CS3.3).*

Disease awareness *amongst the public, if you're going to do that kind of thing it* ***tends to be a public affairs effort rather than a marketing effort, because you can't mention brand****, you know, there are all sorts of rules.* ***But what you can do is get journalists that are interested in this*** *and say 'osteoporosis is an awful silent disease and it kills X number of people and [a celebrity] has it and is the chair of…' so* ***you get a celebrity type situation and they actively write up their stories*** *and …I think* ***when we did the research we were getting about 6% of patients were actually requesting treatment,*** *they were actually asking the doctor 'Am I osteoporotic?' (CS1.3).*

7.2.3. Media role

The media were perceived as having the potential to rapidly and efficiently reach a wide target group of both patients and prescribers and can also be targeted to access people most likely to be affected by a particular condition. Set against this, some respondents considered such coverage as difficult to control (compared with advertising which was considered a controlled means of dissemination), and depending on the media's agenda in a particular situation, respondents indicated it may have either a positive or negative effect on diffusion.

There was obviously a lot of attention at the time with media*. And so* ***it gives that initial boost of patients going in and knowing what they want and asking for something,*** *which obviously drives things a lot (CS3.2).*

If you ***take ED as a whole****, we* ***hardly get any information which comes down which motivates people to come forward****, but you get* ***one splash in the media and it makes a big difference****. You look at these things for* ***motivating men on cardiovascular, you've millions and millions going in publicly to make this happen. But men still aren't particularly coming forward. One little splash and this happens*** *(CS3.2).*

Viagra, maybe not at the outset, but became sex, money and politics which are the three things that drives the media *in my opinion, you know that's a gross oversimplification, but it was certainly sex, and this was…one has to kind of remember you know, I guess, dimmed with time, but* ***taking a pill***

that cured, in inverted commas, your impotence was; people hadn't even been able to conceive that that might be possible *(CS3.1).*

There's lots of different ***audits out there that tell you what's the best form of media****. So if you're* ***targeting 40 to 60 year old women, then you will be aware which magazines they tend to read, on television what times of the day are they most likely….so you know the TV-am slots or Richard and Judy, things like that where Dr Chris Steel might be on and there might be a topic of osteoporosis*** *and so you try and target your media or whatever it is that you're going to do, and newspaper articles. A lot of companies use patient associations, so in this case the Osteoporosis Society (G1.2).*

The uptake wasn't as significant as we'd expected*, I mean if you look on this chart here you've got tadalafil and* ***that angle of growth was massive compared to ours****. They were in a [red top newspaper] as the 'Le Weekender', and so they really got their duration of action which is their USP,* ***they got it out in consumer media significantly over the preceding year****,* ***so they warmed the market up, anticipating a new PDE5 inhibitor, a new treatment for ED****.* ***We made a decision not to do that, so; and then they launched six weeks ahead of us, so the idea was, we were going to race them and hopefully we would have taken off with a flying start*** *(CS3.3).*

The perception that the media however has to reflect emerging big news items, however, makes planning coverage an uncertain business. This was exemplified in the PDE5 inhibitor case, where interest in the topic was displaced by current affairs.

The other thing was that ***at launch*** *it was at the time when we were just about to embark on the* ***beginning of the Iraq war, so a lot of the consumer papers were focused on that happening****. I think the* ***week of launch*** *you know, like the* ***first 12 pages of every newspaper was all about the Iraq war, and any new technology or health technology was just not of interest to them*** *(CS3.3).*

If what is reported misrepresents the product, it creates a very frustrating situation for Industry as respondents indicated there is little they can do to redress the balance due to the restrictions imposed on communicating directly with the consumer. While this was acknowledged as an issue, it was also recognised by respondents that it still has an effect by raising awareness.

Richard and Judy did a three patient study on their show*. You know, so they gave three people Viagra and* ***they said it worked in two, so therefore it's about you know, it's effective in two thirds of the people, and here we are with, as I remember now, 21 randomised placebo controlled studies with 3,000 patients in, and we weren't allowed to talk about that*** *you know, and so we were endlessly on the back foot and we were caught on the back foot as well, you know,* ***we had a media department of like, two people*** *or something you know,* ***we're a pharmaceutical industry, we'd never communicated really before, and so you know, we were doing our best to at least try and get some sensible comment into newspaper stories*** *(CS3.1).*

There was this ***guy who'd done a study and claimed that it was affecting sperm motility*** *and I looked; and* ***it was written up in [a tabloid newspaper] or something like that, just one column, and I remember reading it and I worked out what he'd done, and he'd used 160,000 times the adult dose***

in this study, you know, and this was the kind of nonsense that we were getting, but we couldn't respond to it *and so; and we* ***knew this was going to be triggering all sorts of restrictive practices in the NHS because in the absence of any information from Pfizer or the volume of information that they were getting from the press, they were going to assume this was going to break all kinds of financial records*** *and so that was very influential but of course the* ***positive aspect for us was that everybody knew about it. 100% of the public; it was from nothing to icon in about, a couple of months*** *and it was absolutely stunning (CS3.1).*

With the Boots thing, now that's an interesting one, because it's not actually over the counter is it? ***'You can walk into a pharmacy now and get Viagra over the counter', is what hit the headline. But actually you've got to go into...only one of those three pharmacies in Manchester and it's by patient group direction,*** *and when you look at the patient group direction, you had to not have diabetes and not have raised blood pressure and not have a psychological element and not have...****when you whittle it down, there's hardly anybody that will qualify. But the amount of PR that that generated was massive*** *(CS3.2).*

7.3. Market Leadership

An analysis of respondents' views indicated market development activities assume a higher priority in a company's strategy when a drug holds the market leadership position. Market leadership can be conferred in two contexts: either as the first entrant to a class where there are no other competitors, or alternatively as the one that possesses the greatest market share. There was a sense that respondents believed that their drugs had the capability of achieving market leader status based on the benefits offered by their innate characteristics, but yet they were acutely aware that the market conditions at the point of entry may prevent that aspiration.

Share is obviously important*, I mean it's* ***unlikely that we would be hugely proud of being number 2*** *in a market place,* ***in the areas that we choose to build up a capability in****, and I think that's an important element...****We would never, for example, have invested in risedronate if we did not believe it had the right to be a market leader. Do we expect risedronate to become market leader****? I think that's* ***very unlikely*** *because we're now in a generic sized marketplace where our competition is no longer Fosamax (alendronate).* ***Our competition is generic alendronate and in fact it isn't even a competition any more*** *you know. I think* ***to maintain and grow some share is realistic, but I don't think it's going to be realistic to reverse market leadership*** *(CS1.2).*

I don't think we ever expect to be number one *you know,* ***by the time we'd probably get any closer to that, Viagra will either be available over the counter or off prescription*** *(CS3.3).*

Respondents indicated, implicitly, that market leaders had a duty to further develop the market. The sentiment is not entirely altruistic, as a greater market share delivers

more prescriptions in an expanding market. Conversely development activity is likely to be stopped if results are of no direct benefit to a company.

Until you have market leadership, or until you are close to market leadership, the idea of market expansion is generally of very little benefit *(CS1.1).*

As soon as you've got over 50% of the market you can gamble*. It is a gamble, but it's a valid one****. For the next 100 patients that come in you will get X percent of that, so you will get a bigger share of it****, so it's* ***money well invested*** *in the market* ***to look for patient case finding*** *(CS1.3).*

At the point where we took market leadership, I think, your attitude to the market changes because at this point [early phase of lifecycle] you are trying to penetrate the market. You've got a market share battle with the competition and your goal is to take share*, you know,* ***it's the market leader's job to lead the growth of the market****, and as I've said before, that market leader didn't have any ambitions in that way, they would argue probably differently, but I would say that they didn't demonstrate anything. But* ***when we got market leadership our job was then to increase the number of patients treated*** *(CS1.3).*

We put a lot of time and effort behind getting people to come forward and seek help, but still most patients are getting Viagra, *so you know, at the end of the day you've* ***got to start thinking, well is it worth our while expanding the market for 50% of that market to be prescribed Viagra*** *(CS3.3).*

A sense of responsibility is placed on the market leader to provide solutions to issues that can be potentially detrimental to the entire class. The example of the physical health issues in the AA case highlighted how in attempting to distance the drugs or class from being the cause of certain adverse effects, and instead pursuing the argument that those symptoms were a feature of the disease, there was still a role for Industry to intervene to improve the health of these patients through supplementing services (see Theme 2: Clinician/patient experience; subtheme 2.5: Industry response to experiential barriers). Ceasing these activities on patent expiry does however, diminish the argument slightly that these activities are patient-led as opposed to commercially-led opportunities.

Talking about acting as market leader, ***we try and invest a lot back...on education and on services*** *that will help manage in this case patients with severe mental illness (CS2.2).*

Even though we had this massive growth in the once weekly, if you look at the market again now, ***the number of new patients is flattening off again because there's lack of promotion in the market, because it's become genericised****. So the danger is that need to actually increase the number of*

patients in the market that were actually being treated effectively. It's ***a real shame really in a way because effectively what we've done is halted the market, so potentially a lot of patients are going to remain undiagnosed and undertreated*** *(G1.2).*

Respondents considered that the actions that embody a market leader are important as they influence the way they are perceived by their competitors. Expectations are for heavy investment and addressing issues of policy, safety and NHS infrastructure that are detrimental to the whole class. The interview data suggested that a market leader that stays in market share mode is not perceived in a favourable light by its competitors.

You can be the market leader and just take your sales or you can be the market leader and try and lead the way from education and service operators. I think we try and make sure we do both *(CS2.2).*

There was a need for us to write a ***'dear doctor' letter****. Well then you see your* ***competition, some will walk away from that, and say 'that's going to be really bad news for growing this mark****et' and* ***some will say 'that's great news, I'll keep my market share',*** *so it depends on whether the* ***motivation of the competitor is market share or market expansion****.(CS1.3).*

While recognising that market development fulfils their own needs, respondents also tied the concept of identifying additional patients or 'case finding' into clinicians' priorities once they have become comfortable with a drug. Whatever activities are employed, respondents indicated that 100% market penetration is never expected within the patent life of a drug.

Once the product's been used*, and in the market for a while, and you're* ***starting to see some adoption, you know, real use of the product****, you can then compliment your marketing activities with other …you know, within the later phase of the lifecycle of the drug, given that you've got 10 years, you know, you've got the early launch and growth,* ***how do you then drive greater growth and greater penetration and use of the drug. Typically of the drugs that are accepted, the doctors are comfortable using it, they're seeing the benefits of it in their patients, then they're probably looking for help in finding cases*** *in supporting the use of the drug so that 'how do I find more….how do I do more patient identification? I know I'm not treating everybody, how do I know I want to treat a lot more patients because I see the benefits of it, so how do I get them?', well then* ***that can be supplemented with programmes of support for audit and audit design so that the doctors can trawl through their patient lists and say 'ah yes, these are all at risk'*** *(CS1.3).*

I've ***never seen any market where we've got to within 10 years of entering a new class of drugs, a new disease area where we've got anywhere near saturating the market in terms of penetration****. And in there you've got a* ***mixture of people who should be taking it and some that shouldn't, you know, because the docs have got it wrong and all the rest*** *(CS1.3).*

*We spend a lot of time thinking about **how do you get them [clinicians]** to be a bit more active in their intervention and **checking and evaluating the patient to identify the opportunities** (G1.2).*

7.3.1. Corporate philanthropy: Subsidy of health services

A market leader development strategy may involve funding initiatives in the health service to identify eligible patients that the NHS would otherwise be unable to support. Respondents discussed how the provision of those services may be necessary to assist in connecting the dots between diagnosis and treatment and removing the bottlenecks to prescribing, as demonstrated by the introduction of the Fracture Liaison Service subsidised by Industry to identify patients with fractures in the BP case.

***In some markets it's important to have everybody DEXA scanned, in order to be able to prove they're osteoporotic**. Well, there's **just not those facilities available on every street corner** in this country. We just **couldn't fill the gap**, I mean it's just too massive, so you **had to find other surrogates of what is osteoporosis** and hence when you see it in guidelines now, you know, it's basically if they're over 65, and had an incidence of a fracture. So **that's why the fracture clinics became really important**, and the fracture register became important, because **you needed the secondary care centre to tell the GP 'this person has had a low trauma fracture, they're osteoporotic, treat them'**(CS1.3).*

***We were aware of MSD's fracture intervention clinics.** I mean they were coming from the **position where they had the market dominance in terms of the share at the time, and their question was really an issue of can I get people to actually find**… I think that it was very clever, and I think also very valid. I mean we come down to **fracture as one of the biggest causes, and it's the one that we should probably go for the most, and it also makes what is a bit of a fuzzy disease in terms of its definition, something quite solid** (CS1.1).*

*There's very tight governance rules under our code of practice about what we can do, but, in principle, what you're doing is **providing assistance to support the doctor's objective** of what he wants to do and you **don't couple any of those services with the prescribing of the drug**. **What you do is provide the service and if the doctor's chosen your drug well good for you and that's really down to you and your skills of selling the drug to the person in the first place** (CS1.3).*

The provision of subsidies, while portrayed in some regard as corporate philanthropy, is usually dependent on more patients being identified and is often time-limited, usually to coincide with the patent length of the drug concerned.

Respondents indicated that ideally the aim is to partner initiatives that have a strategy in place for the service to become eventually self-sustaining.

At some point quite honestly we have to say that if we're providing blanket support services, even though we would never ever do anything that would try and…you know, ***we would never link a service to any kind of prescription requirement, but at some point you actually look at it and you say 'for every dollar I'm investing into scanning, I'm getting 50 cent back out', I mean I can't do that for very long because that would….I mean for every dollar in I should at least have to make a dollar out and if I don't do that then I'm not going to be here*** *(CS1.1).*

I think every company used to do that sort of thing, to be the….as a gesture of really goodwill to the communities worked in. ***Nowadays we think much more like 'okay, what's my exit strategy out of that funding****?' as I give it to you let me work in partnership about how I actually…****my objective is to fund you enough so you won't need another funding.*** *I think the objectives should be unless you're going to make a long-term commitment to be in it forever, which****, given that we have a nine year patent life usually, eight to nine year patent life in market, it seems unlikely that I'd want to fund you beyond that patent expiry*** *(CS1.2).*

7.4. Research: New Indications/New Formulations

Research into new formulations was perceived by respondents as a market development strategy that widens the appeal of the drug so it can be used in more patients, such as in the BP case with the introduction of the once weekly formulation.

Patients that have previously tried these drugs and dropped out because they didn't like the regime and it's unpleasant*, blah, blah, blah, and they said 'well look****, now I can come back and I can start again and I can comply with it****', so I think you've got that. You've got an extra period there where* ***more patients took the drug for longer*** *than they did in this period, so that would add to the sales curve, because if a patient is only taking 6 months-worth but now they take 10 months-worth in any one year, you can get a 40% increase in sales per patient. So you got that, and* ***you got real market expansion because the doctors gained confidence****.* ***They said 'now I can see the patients, I always thought they would never be able to take these drugs', but this one they can give it to them, so they had confidence in doing that. And that drove a complete change in attitude to the use of this class of drugs*** *(CS1.3).*

If clinical need however, is not a driver then it was perceived by most respondents that these 'life-extension' strategies are unlikely to significantly influence diffusion. This was highlighted as a reason by some respondents in the AA case for the lack of impact of dissolvable formulations.

People will try strategies of trying to extend the life of the drug in other forms. ***New indications don't really help you unless it's a very specific dose so that the dose won't be made generically****, but an extra indication and the drugs available generically, it's still going to get dispensed generically so you're not going to get any extra life out of that in this market. So life extension strategy…****new formulations are modest in their success. Some are good, where they're slow release and the BNF have decreed that it has to be done this way because there's real patient benefit,*** *but there are* ***relatively few of those*** *(CS1.3).*

I think the Velotab, ***the rapid dissolving formulation****,* ***that again met a small unmet need for certain types of patients which I think did differentiate Zyprexa versus others on the market at the time*** *(CS2.2).*

There's a ***Quicklet form which is a dissolvable form****. People* ***took to it to a certain degree, but not massively*** *because we* ***didn't have data to show that it had a faster onset of action****, so it was just a an alternative formulation really, it was* ***more convenient for some people to take****. So it* ***didn't have a great impact****, and the injections had much more of an impact. (CS2.1).*

In some instances, the relative advantage offered by a new formulation or a new indication at later stages of the lifecycle can be such that the rate of uptake can mirror that of the drug's initial introduction to the market (as was the case for some of the AAs on gaining a bipolar licence). A few respondents highlighted however, that there is a greater imperative with extension strategies to reach the market first in order to capture the market share. The impact that competitors offering the same indications or formulations can make at this late stage was thought to be far more diluted than what was possible with the original indication.

Olanzapine also got a bipolar licence faster than we did*, which is something that they did quite well, so when they launched they launched with one indication which was schizophrenia, but then they got another addition to their licence which was bipolar, and* ***it took us longer to get the bipolar addition to our licence, even though we were first on the market, so they'd done a better job at actually, you know, constructing their clinical trial programme,*** *and I think that* ***helped to drive some growth as well for them*** *(CS2.1).*

New formulations were also thought to help protect companies from the effect of generics entering the market. Respondents indicated how patients can be switched back to branded medications if the new formulation offers substantially favourable benefits.

Previously this was all tablet use, and then in, August 2002, ***we launched a long-acting injectable version of Risperdal (risperidone), which again was the first atypical injection in the marketplace. It was eagerly anticipated****, because one of the big* ***problems with oral medication is compliance****, so patients who have schizophrenia often don't have a lot of insight, so they don't think that they're ill, so when they're in hospital they can be encouraged to take the medication, but* ***when they're back in the community and not supervised, they often don't take the medication, and that means that they're far more likely to relapse****. So, with Risperdal Consta they have to have an* ***injection*** *once every two weeks but that then* ***gives them medication cover for two weeks****, so it was a combination of the older depot type medication which were injections, with the new atypical medication (CS2.1).*

7.5. Dispensing/ Supply Issues

Compromising the supply of a medication was thought to impact on the uptake and diffusion of a drug and yet it is not often recognised as an influencing factor in pharmaceutical diffusion outside of the Industry literature. Interviewees described several scenarios including the sometimes challenging logistics involved in supplying to levels of demand, counterfeit medications and the presence of illegal imports through parallel trade that had a bearing on the diffusion of their drugs.

They'll have ***ensured that the product was stocked in*** *and it was early stocking in so there* ***wasn't any delay in availability. It's that sort of 18 months prior to launch*** *that really starts digging into our own marketplace and mapping it out and* ***how will we train and how we get it stocked in and we go down to the weeds really of implementation*** *(CS2.2).*

It's a very complicated environment, these days because of course the one thing we haven't talked about is that ***an enormous proportion of the supply of Viagra, in inverted commas, is over the internet****, which won't be reflected in those figures. A* ***proportion of it is counterfeit****, but it's virtually impossible for us to gauge how much. So* ***there will be imported Viagra that's used in the UK, there will be fake Viagra and then there is this whole range of other sort of pseudo-Viagra treatments*** *that you'll have heard of that complicate the picture as well, so have we reached our growth peak? Well,* ***if we can continue the efforts that we are currently putting in place to try and combat counterfeit use and you know, illegal supply and so on, then they'll be the prospect of higher sales in the UK*** *(CS3.1).*

8. KEY OPINION LEADERS (KOLs)

Opinion leadership support was a theme that all respondents emphasised was influential in the diffusion of a drug. Key opinion leaders (KOLs) were described as clinicians who as result of their experience, technical competence or social accessibility are experts in particular fields and are held in high esteem within the social system of the clinical community. Respondents conceptualised them as having innovator adopter characteristics and occupy a unique influential position at the centre of interpersonal communication networks through which they can convey their influence.

Interview data indicated that providing KOLs are seen to remain independent, they were thought to exert their influence in two ways at various stages of the drug lifecycle; firstly as advisors to Industry and secondly as advocates for certain treatments amongst their peers. Through these two roles their involvement spans throughout the lifecycle of a drug, from before launch as clinical trial investigators, through to raising disease awareness, generating consensus agreement in disease management, education of peers, message reinforcement and market expansion.

8.1. Early Engagement/Collaboration: Advisory

The involvement of opinion leaders at early stages of development was considered important in gaining their support. Early engagement with Industry gives KOLs privileged access to exclusive information and an understanding of the data, which supports their credibility and esteem. Interviewees stated it is a somewhat symbiotic relationship in that it extends the opportunity for KOLs to influence trial design as co- or lead investigators on studies.

*Well **key opinion leaders play a very important role**, and I would rank them number 1, because they tend to get **involved at possibly even Phase I stage**. Because they will often be using multicentre trial based sites, and they will often be the **people that are leading that research**, so they will be involved with our researchers, often long before the marketers get anywhere near it (CS1.3).*

***Endorsement** is one of the key things we look for at product launch to ensure that the **key names** in psychiatry or whatever disease area you're going into**, understand our data and could place X appropriately**. It has a lot **more credibility**, we have **investigators standing up on the day of launch saying you know I've been involved in the trials, these were some of the results and this is how a patient did** (CS2.2).*

*Many of the **key opinion leaders** have been involved but they were **involved in the studies through Phase II and Phase III**. And by being involved in the studies they were involved, albeit in a blinded way, to the medication and **involved in some of the early study manuscripts prior to formal publication** (CS2.2).*

Several views were expressed that suggested early engagement allows KOLs to gain their early experience of a drug in clinical trials. Respondents suggested that those trials regarded as having the most significant impact on diffusion were ones involving KOLs in that field, as their association gives the trials enhanced credibility. Input from KOLs also helps Industry best understand the role of their technology in the broader management of a disease and any potential sensitivities that could surround its introduction.

*We had a set of **very clear messages about how we viewed this condition** which was obviously **done in concept with those people who had been treating it for years**, because I mean you know, to recognise that some people had been you know, professionally trying to treat erectile dysfunction and then along comes Pfizer and there's a sort of you know, we **didn't want to sort of make it look like we'd arrived, now everything was okay** (CS3.1).*

*We work with a faculty of people which is about 20 specialists drawn from general practice, urology…all the kind of **established authorities if you like in the field**. They were the authors if you like and certainly **if not the authors, certainly the reviewers of all the educational material that we put out for GPs and nurses and guidelines** and any patient information and all the rest of it, and that was important you know to have, if you like, **peer credibility** but it was also important that we, to be frank, that we **completely understood the area**. You know, **we needed to demonstrate that we weren't going to just rock up into what is a sensitive condition that can be multifactorial and just flick people some tablets and say there you go, that does it doesn't it**? (CS3.1)*

The Industry indicated that the value of advisory boards, sometimes involving KOL input, is to guide the content of a company's education and promotion materials. They have a unique insight, which Industry lacks, enabling them to gauge their

peers' receptiveness to their messages (see Theme 6: Communicating relative advantage and Theme 7: Market development due to the linkages to message clarity (subtheme 6.2.1.) and market research functions (subtheme 7.1.) that KOLs influence, respectively).

*The **KOLs tend to be on the advisory boards**, they would do more high level, look at **the quality of your science**, look at the **quality of your studies**, **tell you which ones you should use and how it supports your message** and your marketing strategy and then you know the individual psychiatrist, what we would call the more jobbing side, who do the day job, they tend to come to focus groups (CS2.2).*

Respondents from the BP case study indicated that when there is an innovation in a developing clinical field, a situation may arise where the expertise may only exist within the company. Those people then become responsible for leading the field and building networks of influence. Interview data suggested that in the BP case, such close associations with the manufacturer did not appear to damage their credibility as they became recognised as established authorities on osteoporosis. The loyalty that was then afforded to the originator company however, was highlighted as a barrier to access for competitor drugs, creating a scenario of institutional inertia.

*I think the advantage that we have in that is that **we were there at the very, very beginning** because you could say that **the key expert was someone inside of P&G** and they also…I mean the way we run our company, we are a very commercial company otherwise we wouldn't be a successful company, but that is we don't believe that should be at the expense of great science, and again as I say we're a science company by background, **so these people had the opportunity to build really established relationships on a high level of trust, with those key opinion leaders**. I mean **they felt like very much co-collaborators**, and I think that was pretty unusual even in the day, **a different model that I think is getting more common now**, but it was a little bit ground breaking (CS1.1).*

Respondents believed that KOLs do not necessarily have to come from within companies to show allegiances. The cases demonstrated that if companies develop strong relationships with leading experts in the field, through support of research, or assisting in raising the profile of a disease, when a new competitor enters the field,

loyalty may manifest itself as scepticism towards the newcomer. Respondents explained how establishing trust between new entrant companies and KOLs requires delicate handling over many years for competitors to gain recognition. In this sense, scepticism, whilst overtly indicative of a conservative approach to claims made about new drugs, may according to respondents, be used to almost validate or rationalise loyalty issues.

We were promoting ***this directly to key opinion leaders and GPs principally at this time. Key opinion leaders were very loyal to the competition****, because you know, they said 'the* ***trade-off here is not great enough*** *so I'm going to stay loyal to the competition' and this particular group of opinion leaders are, because* ***it's not a big field, there's not a lot of drugs in it, they tend to be loyal to those people that have supported their research****…it was a* ***heritage factor*** *involved in that (CS1.3).*

There was a ***scepticism of the new person at the table****. So I think there might have been a period of time, and sadly it looks like that can, you know, not surprisingly* ***last three or four years before they will actually trust you*** *And so maybe there's that element where I think they didn't shift because they didn't necessarily give …maybe they had an* ***access problem to the people that were influential*** *(CS1.1).*

8.2. Hierarchical Cascade of Influence/ Peer Credibility: Advocacy

An analysis of respondents' views indicated it was important for them to be aware of the hierarchy of influence that exists amongst KOLs, those with the most established reputations internationally having the greatest effect on diffusion. Their messages are viewed with trust and authority and diffuse down through the tiers of influence to change the clinical practice of the many.

You've got to understand the network of opinion leaders and understand the diffusion effects that opinion leaders have in their local network, say who respects who, who listens to who, whose opinion counts? *And that's* ***an exercise which we have to understand*** *who to talk to about a particular medicine (CS1.3).*

KOLs are the thought leaders of where patient care, disease management should be going. *So you've got to interact with them. You've got to* ***keep ahead of what they're going to be telling people at congresses*** *(CS4.2).*

Whilst most KOLs are typically secondary care specialists, the important factor is who initiates treatment. Non-clinical actors are also important in deciding what drugs can be accessed through formularies. Failure to understand the interaction of all actors was thought to potentially have a detrimental effect on diffusion. The misplaced assumption in the BP case that GPs were able to act independently of KOLs, was thought to have led to a scenario of total lack of KOL support. Similarly, a plateau in the diffusion curve of one of the PDE5 inhibitors was attributed to scaling back sales force activities in secondary care to focus on primary care, not having appreciated the impact specialists had on GPs prescribing behavior in this field.

Our market understanding of the behaviours in this field were flawed. We ***underestimated the impact of the opinion leaders versus that of the GP****. I think we went in with the* ***perception that the GP would be able to identify the patients and just willingly treat and couldn't give a damn what the opinion leaders said. Well actually it's completely the reverse****, and we didn't have a great deal of opinion leader support through this period, largely because of the way we entered this market. You* ***have to get them on side so that they feel engaged and involved with how patients are treated in the community, because, at the end of the day, they pick up the mess for wrong treatment elsewhere****, so* ***if they're not engaged with that they will argue themselves into a position where they think you're wrong****. I think we in hindsight we got that wrong, but we got it right through this period because we overcame all the barriers, they could clearly see the advantage that they would be able to treat patients more freely and easily, and give GPs more confidence in being able to initiate therapy (CS1.3).*

The belief amongst respondents was that credibility is essential to maintaining a KOL's position in the hierarchy of influence. Their status is dependent on them being viewed by their peers with an element of trust, and by being transparent about their relationships, their position as advisors becomes a credible one. Their ability to manage conflict of interest was highlighted by respondents as a feature which enables KOLs not to compromise their credibility, whist maintaining a relationship with Industry.

*I think if you can **motivate specialist care to be able to talk to GPs and give their professional opinion**, then that's going to be of far more ...not power, but relevance and it's **far more trustworthy** because they're the specialists. This is their area that they specialise in. So even as an influencer, you've got to respect that cascade of influence (CS3.2).*

*We had **relationships with all of the individuals [KOLs]** that were there. **And so did all the other companies** as they were coming in, and that's again just the nature of…**if you were looking for the expertise that's where you would gravitate**, I don't think that's that unusual. But I think I will be really honest, I've never seen in all of my experience in dealing with any of the people at that level, have **never actually seen them have any major issue with managing a conflict of interest**. I think they're aware more than anyone else, **they understand the old maxim which is, it takes a lifetime to build up a reputation and one night to lose it,** so I think they really understand that (CS1.2).*

Adopting a position of neutrality was thought to be a means of maintaining their position of credibility amongst their peers. The only circumstance in which the respondents suggested KOLs will take a preferential position on individual drugs is when there are no other competitors in the field. Some respondents highlighted the impression of impartiality can raise the issue internally of what tangible benefits they can bring to a company, but their influence is subtle and mediated through raising awareness of a disease. This impacts on all drugs for that condition and appeared to justify their value. Respondents explained that KOLs have to maintain a fine balance, as the respect in which opinion leaders are held was thought to be easily lost if their views are perceived as being too closely aligned with those of Industry.

*I think KOLs are important in driving the sense of why you should use a statin. I think **getting a key opinion leader to say oh you should use this statin over another statin is quite difficult. But I think the key opinion leader's role is to say use a statin in this disease area**. It's **our role to make it our statin that's chosen**. Because you shouldn't be expecting people whose job it is to distribute evidence around the health and the disease area to sell our drugs for us, that's our job, that's what we're paid to do (CS4.2).*

*I think the people that manage the relationships with opinion leaders in the Industry are **continually having to justify to more commercially minded colleagues why would we be investing in these individuals** from the amount of time that we spend with them, the amount of information we share with them, when they **actually deliver tangibly so little**. Because in a competitive marketplace with more than one product **they're the last people to take sides**. It's not in their interest to do that because it **would start to jeopardise their relationship**, they will only ever do slight preferential positioning based on the real solid data that they really understand and that they're signed up to. **The only time when you would actually get them taking sides is when you're coming into an area that's so new that there isn't anyone else** (CS1.2).*

To maintain this balance, the suggestion from respondents was that KOLs appear to be more reliant on evidence than any other adopter group to justify their position on a therapy as they are acutely aware that their credibility is being judged on the outcome of their recommendations. On this basis, a clear view was expressed by respondents that drugs have to offer true relative advantage before receiving any kind of endorsement from a KOL. Where a trial does not receive KOL support, its impact can be significantly reduced. Respondents believed this was the reason behind the limited impact of the Fracture Intervention Trial (FIT) for alendronate.

I'd put opinion leaders alongside evidence in terms of importance because ***most people assume that the opinion leaders are talking with a good base of evidence behind them****, otherwise,* ***very few actually put their head up above the parapet and say, this is a good treatment, unless they've seen a really good amount of evidence to support that.*** *The notion that you can take them off to fancy places and buy them a fancy dinner and then they'll stand up and say it's the best thing since sliced bread is somewhat over simplistic (CS3.3).*

The ***FIT trial really didn't get them on board there at the beginning due to the tolerability issue****. It was a huge issue and* ***I don't think we'd warmed up the opinion leaders properly****. It happened in other countries, but it didn't happen here, and I think it's just…****huge loyalty from the opinion leaders to the competitor****. We* ***battled to win them over until we got here, and when we got here [once weekly formulation]****…there was such a* ***transformation in how people saw the attributes of the product.*** *It's extraordinary and you will see that around the world that the adoption of 70 milligram was just incredible...a dramatic change in use of the medicine at a critical…at a certain point in the lifecycle of the drug. It's a wonderful product (CS1.3).*

Doctors I don't think saw it as a landmark trial *in the sense it was, but it was never* ***seen in quite that same ethos because there weren't the people there supporting and shouting about i****t in the same way (G1.2).*

The motivations of KOLs were seen by respondents as multifarious. A desire to remain up to date via trial involvement or conference proceedings allows them to maintain an educational role (often reflected in their joint clinical and academic appointments). Additionally driving improvements in clinical practice serves a certain self-interest by minimising inappropriate referrals.

*Typically they [KOLs] are **motivated to try and improve treatment**. I mean they want to use not just the latest gismo because it's sexy, but because it works better. It brings patient benefits and that they want to communicate that and it can make sure that their customers, i.e. their peer group or GPs in particular, use the medicines appropriately and opinion leaders typically are in a secondary care setting, a more academic setting, and so **they like to get out to educate people, not to promote a medicine, but to promote a therapy**. You know, to say 'look these are therapeutic options, these are guidelines, this is where you should use these' because their **vested interest is getting….is preventing inappropriate patients coming to secondary care**. And they are motivated by that. They really want to improve care in the community so that they aren't getting unnecessary cases coming into hospital which could be prevented by appropriate care and by early identification of the patient by the doctor. It can almost sound altruistic, but I think as a general statement that is what does motivate them. Because they know they've got waiting lists and limitations you know, they're well aware of that (CS1.3).*

*When you're talking about the **people that have key influence**, these are the people that are really sort of **shaping the way that people view the disease area** at a country level. Those individuals are really still wanting to **hear the news early**, and probably the earliest the better, because what I think keeps them in their **status as being key opinion leaders is access to information that's not normally available through all the normal channels** (CS1.1).*

A high level of interest and enthusiasm amongst specialists inevitably generates further interest further down the cascade, so that in some cases drugs are well known about even before launch without any form of promotion.

*There was obviously **clinical trials ongoing** and there was **a high level of awareness amongst specialists that here was a more effective statin and if you're going to be engaging in research in this area, well use the best drugs**, I mean they were very interested in atorvastatin and word got out that here was something that was better than what was currently available. We scientifically shared the data that said this is a more effective drug, but I mean, that was not promoted at all (CS4.1).*

Interview data suggested that for drugs mainly prescribed in primary care the influence of a local KOL may supersede that of those on the international stage. However, it is likely that the local KOLs would have been influenced by international figures themselves at an earlier stage.

There are KOLs which are obviously more national and then local KOLs, the local specialists. And what you find is, particularly ***local GPs they have a strong interrelationship and a trust and respect relationship with local opinion leaders****,* ***so, people who they're working with perhaps on a more regular basis, local specialists****. You've got the UK ones influencing the local specialists and then internally influencing the GPs, so, the national ones are not always the best influences of the local GPs directly. There will be* ***different networks and relationships and influence according to the different disease areas****. But the same logic applies it will just be one KOL for one area is not going to be valid for another, so it is* ***specific to the disease area*** *(G1.2).*

Obviously the ***bulk of prescribing is done in primary care****. Your* ***GP will tend to look at their local opinion leaders****, perhaps the local cardiologist or diabetologist or where the GP sees their patients going and what they come back out on. So I think they'll be* ***more influenced by that than say a big national key opinion leader*** *(CS4.3).*

8.3. Advancing the Field Through Collegiate Agreement: Advisory

Analysis of respondents' views suggested that even more powerful than individual KOLs' opinions are those manifested as part of a collegiate effort such as consensus guidelines. Industry indicated that bringing together such groups was an important activity in accelerating diffusion, although it was necessary for companies to remain distanced from the outputs. In conditions managed predominantly by non-specialists, Industry views suggested there is greater reliance on collective specialist views to guide practice, although this may take an earlier form than official guidelines.

I think when you're talking about something where there ***isn't a consensus or understanding****, I think* ***opinion leaders are absolutely critical*** *because none of the bigger third party bodies, you know neither* ***the colleges or the WHO or public policy will align itself behind something that the experts can't agree*** *on, so there is no hope of potential for it until you start building a core nucleus of, or there is a* ***core nucleus of experts*** *that actually can do that (CS1.1).*

We developed I think critically national ***advisory boards of the key, the really key opinion leaders****, so you're talking about a scale of maybe 10, 12 key clinicians in the area in the UK. And what was interesting was that the board that we* ***created was administered and run by us or facilitated by us, but chaired and directed by the clinicians themselves.*** *So we set up something where there was a nominated chair, the chair changed, but where they wanted to go, what they wanted to do, we had a table to say where we thought we should be going, but it was really them …it was a board for them run by them but organised by us. And I think that also was very helpful, because that, when you're in a* ***fledgling field it helps build up a lot of credibility****. And a lot of things* ***sort of sprang out of that, such as the need for Royal College of Physician Guidelines*** *which were developed (CS1.1).*

Well statins are predominantly a primary care drug. The difference is that ***primary care still look to secondary care for the okay*** *which is a bit surprising really. I think secondary care is obviously an early adopter. But* ***primary care look towards people for guidance*** *(CS4.2).*

9. COMPANY CULTURAL HERITAGE/ PERCEPTION

A few respondents highlighted the importance company heritage and culture has on diffusion. Analysis of their views suggested heritage appeared to be a concept not just defined by the specialist clinical areas a company has experience in, but also their cultural background and mind-set, their corporate identity and the impact this has on influencing their behaviour, beliefs and ethics of business conduct. It became apparent through the case studies that companies need to be aware of the various behaviours, relationships and networks of adopter influence that exist in different clinical disease areas. While prior experience may provide a company with an in-depth knowledge of the psychology in one clinical area, the assumption that the same beliefs will translate to other disease areas, however, can be fundamentally damaging to the uptake and diffusion of a new drug. Respondents explained it is certainly not the case of a 'one size fits all' approach, a perception that has been to the detriment of some of the companies interviewed.

9.1. Cultural Influence on Company Perception

Respondents suggested that the culture within which a company operates can affect how people perceive them, as it ultimately influences their behaviour and can influence adopters' decisions. Culture is very difficult to define, but in the inaugural BBC Today Business Lecture in 2011, former Barclays Chief Executive Bob Diamond, suggested that culture can be captured by the values that prevail in how a company or how its people behave when no-one is watching. While some companies are known for an aggressive style of approach, other companies may be more conservative. Interview data demonstrated however, that being at either end of this

continuum was seen as a potential drawback. A company's approach ideally has to be responsive to the specific needs of the disease area into which the drug is entering.

Apart from investor relations media work, we ***didn't do any consumer media work at all pre-launch****. We* ***notified them when we launched****, but as I said the* ***papers were just full of the Iraq war*** *then so they were like;* ***another treatment for ED*** *and they* ***weren't interested****, so I think* ***culturally we were quite conservative…*** *and it was like "****we've got this drug and it's quite good really" rather than being sort of very gung ho and aggressive about it,*** *but that* ***approach can alienate people*** *as well (CS3.3).*

Respondents described how past experiences adopters have had with a company can be important in the diffusion of their subsequent drugs based on their conduct and their claims, especially where positive interactions have built credibility, linking this theme closely with clinician experience (see Theme 2: Clinician/patient experience). Preserving reputation therefore seemed of utmost importance and respondents indicated how companies will employ 'rescue strategies' in order to maintain that credibility if one of their drugs is the subject of controversy during its lifecycle. Being seen to respond to a problem was regarded by respondents as 'good customer service'. While this is possible to do with clinicians, respondents indicated frustration at not being able to defend their reputations directly to patients (see Theme 6: Communicating relative advantage; subtheme 6.2.2: Product awareness).

Then you have obviously I would say things like ***reputation****, you clearly have an* ***advantage if you're a Pfizer or a Glaxo versus a company no one's ever heard of*** *(G1.1).*

I think ***it's experience with the brand and the company*** *and it's about sort of* ***trustworthiness*** *really and* ***creditability****. You know, I think we were* ***known to a lot of our prescriber base****, they* ***knew the data on one of our other drugs, they knew how we'd gone about marketing to them****, they have a* ***view of what our company has to bring from our services and our product perspective*** *and that helps I think, that* ***helps when you launch a new product****. So we often use, we'd call it* ***our heritage in CNS as being a strength for us*** *in our marketplace, we've* ***been around a long time****,* ***customers know us****, you know we've got* ***good science****, you know we tend to have* ***good products*** *and good service offerings (CS2.2).*

I mean you know the ***people*** *that are* ***real advocates of our brand are generally people who'd had a bad experience, tried it again,*** *and I think there are lots of examples there and I think it's that we know that on average if you as a consumer goes into a restaurant and has a good experience, you will probably tell one person that you've had a good experience in a restaurant. If you have a bad experience, you are likely to tell quite a few more people that you have had a bad experience, but* ***if***

***you have had a bad experience and then somebody did something to resolve that for you, you will probably tell everybody what great service you've had**, so, and that is quite a common thing in customer service, so actually there is a, not deliberately because we would have much rather got it right to start off with (CS2.3).*

Analysis revealed that a company's culture can dictate a particular mindset of approach that while suitable for some disease areas, may not be transferable to all. Diffusion of healthcare technologies is a socially complex process and it was acknowledged by respondents that it is the role of the diffuser to understand the behaviours and the expectations of the people they are interacting with in order to influence that behaviour. Heritage was perceived as being important by some respondents in gaining an understanding of the social etiquette that exists in specific disease areas that can save time and resources in future ventures in that condition, but others felt that there was no guarantee of a favourable response.

*I think we made some mistakes at the start. We **culturally and historically** have always been a **strong cardiovascular house**, and I think the **mindset internally** was **'well everybody behaves like they treat cardiovascular disease', well they don't** (CS1.3).*

***Our heritage** is, you know, back through the days of Prozac and even before that. And so **we knew who is who in the area of psychiatry**. But at the end of the day if you **haven't got a medicine which offers true values it doesn't matter who you know and what you've brought to the market in previous generations**, you know, a product isn't going to be sold and used just because you've got some presence and heritage. I think it **can give you a head start in knowing who to talk to** and, for example, who to involve in your trials and who to go to for an opinion. But these individuals **aren't going to give you an opinion which goes against their own personal experience and beliefs** (CS2.2).*

*So **we knew how GPs worked** and we knew; I guess you'd say **organisationally our capability was in primary care** (CS3.1).*

9.2. Culture Determining Company Priorities

Analysis of respondents' views suggested that cultural ethos can have a direct bearing on a company's priorities. Whether that priority is market expansion or market share, in their opinion is a direct result of whether a company's cultural

mindset is driven by maximising revenue or sales, which is dependent on the founding principles on which the company evolved.

> *We're a **research based** pharmaceutical company our **goal is market expansion**. We introduce drugs into **areas** where there's **under treatment or poor treatment** available and go in and **try and treat as many patients as we can** so we're improving health. So it's a very **different mindset to companies driven by market share**. So that's a **cultural thing**, mindset (CS1.3).*

The pharmaceutical market differs from other consumer markets due to a relatively short period of patent protection. Yet some companies operate within this market with consumer-led priorities, which can result from the influence of other arms of the company if it has multiple business units spanning several markets. Respondents indicated how this feature can manifest itself in clinical trial programmes, as they may be designed to achieve outcome measures commensurate with a particular cultural mindset.

> *What has changed is that the **time horizon for products to actually be able to recoup their initial investment** has proven and definitively become that **much shorter**. I think there used to be strategies that companies could have to develop and to create variants of molecules and new formulations that kept their patent protection in existence, but **generics are now challenging drugs well before they come off patent**. The problem with our philosophy at that time was **it's a long time to wait for a market when the market can build slowly and can disappear quickly** and I think one that we struggle with sometimes is that in the **fast moving consumer goods world we're used to building enduring and lasting brands**, so in our portfolio we have 60 brands that have been on the market for more than 50 years (CS1.1).*
>
> *The interesting facts are in different markets people **behave very differently depending on their mindset of whether they're a revenue maximiser or a sales maximiser**, and they will **design their trials** probably to give them a **predicted result which will fit with that position** that they are, their behaviours. As I say, we will typically design everything to try and expand the market to try and get more patients treated (CS1.3).*

A company's heritage impacts on the level of priority assigned to a new drug and the accompanying level of investment it receives. Respondents suggested that in companies with diverse portfolios of drugs, certain drugs will be afforded a lower priority, which impacts on its rate of uptake, compared with those drugs that form the single focus of a company and receive substantial investment from the offset.

People would recognise *that within the* ***key areas in which we specialise*** *that we often have* ***some of the leading brands****, if not the leading brand. And we tend to often* ***invest in classes of drugs, rather than have just one in a particular class****, so we become, if you like, a sort of* ***specialist within that area****. So quite a lot of say something like HIV for example,* ***our representatives and our opinion leaders and our researchers are right at the forefront of those therapy areas****. And so I think quite often we are involved in being at the cutting edge and* ***people value that*** *(G1.1).*

Lilly *are a company that have had a lot of drugs and have a lot of* ***heritage in psychiatry****.* ***AZ doesn't,*** *whether it's Astra or Zeneca. So if you think if we don't have any other mental health drugs at all, you know, you go through you know Prozac is a* ***Lilly*** *drug, they have other things, it's their area. They probably* ***had existing relationships with the customers*** *and to be honest, whereas you know* ***olanzapine was probably a big priority for Lilly****, if we go back to you know, '99, 2000, 2001* ***was Seroquel such a bit priority for AstraZeneca?****(CS2.3).*

When companies merge, partner or reassess priorities, respondents expressed the view that any increase in resources that means the message can be conveyed more efficiently to an audience will help to increase usage, but where to allocate the resources most effectively is dependent on what the message needs to focus on. Differentiating between products in a market is managed through sales force presence (see Theme 6: Communicating relative advantage; subtheme 6.2.3: Product justification (representative detailing)). If however, inadequate diagnosis is the barrier to diffusion, other strategies such as disease awareness programmes (see Theme 7: Market development; subtheme 7.2: Raising disease awareness) and thought leader consensus around guidelines (see Theme 8: Key opinion leaders; subtheme 8.3: Advancing the field through collegiate agreement) were thought by respondents to be of more value to increasing a drug's diffusion. Mergers and partnerships may however, dilute the impact of any one culture dominating in the approach.

Parke-Davis was a tiny company *really, it was part of Warner-Lambert which was a medium sized company, but I mean the* ***pharmaceutical arm was relatively small*** *so much so that one of the things that was done pre-launch was the* ***striking of the partnership with Pfizer to co-promote*** *the product (CS4.1).*

Any culturally different approach from Bayer *should have been* ***balanced out by the GSK*** *side of things I suppose (CS3.3).*

Respondents indicated that understanding the culture, and therefore, the likely approach of competitors was important in devising their own marketing strategies (see Theme 6: Communicating relative advantage; subtheme 6.2.3.1: Competitor objection handing).

> *There's a bit of **Goliath and David** going on. You know, **they are much bigger**. They have **far more people**…it's one of those things, **do you box clever and play to your strengths** or, you know, stand behind your product, **or do you try and play their game**? And I guess **where we've tried to play their game previously, it doesn't work**. It's not something which you can win on 'cos, you know, **they can change 5% of their field force and out-shout us tomorrow**. We'd have to change like 25% of our field force to be able to have that magnitude of change (CS3.2).*

There was an appreciation from respondents however that a heritage in a particular specialty does not necessarily equip them with sufficient knowledge for subsequent products. Even in a distinct specialty such as mental health, the potential diversity of conditions covered which can be managed both within the primary and secondary care settings means that each new drug requires subtly different approaches to convey messages effectively.

> *Janssen have got a **good track record in psychiatry**. **Prozac was our heritage before Zyprexa but a lot of that was primary care**, we had consultant psychiatrists, again it's different, it's **very different launching SMI[22] than it is with depression**, so yes they knew us, whether we had I would say expertise within that area I don't think **so**, I think it's a different molecule and a different need, junior doctors treat a lot of depression for instance whereas consultant psych tends to deal with SMI. So yes and I **guess we had presence and we were known**. I'm **not sure we had necessarily expertise in the schizophrenia** marketplace (CS2.2).*

Ultimately, not having a heritage in a particular field was not perceived by respondents as posing a barrier to a new drug if it offered relative advantage. However, crossing over industries without having the basis of a pharmaceutical heritage can mean operational knowledge is lacking that may have a major impact on

[22] Severe mental illness

diffusion (see Theme 3: Evidence; subtheme 3.2.4: Journal quality/publication control).

*I think yes, a **history in psychiatry probably helps**, Lilly and Janssen Cilag are both seen as having a long history in psychiatry, so I think yes, it probably helps but I **don't think it would stop a new company coming in with a very good product** and doing well in the marketplace (CS2.1).*

10. PRICING

Discussions on pricing strategies attracted an understandable reticence from respondents, exacerbated perhaps by the fact that the price of branded pharmaceuticals is set ultimately by the Pharmaceutical Price Regulation Scheme (PPRS)[23].

10.1. Price Setting

Analysis of respondent views suggested that whilst a number of factors are at play in price setting (recouping costs of R&D, remaining period of patent protection, impact of parallel imports on profits), it is ultimately governed by what the market will bear. What the market will bear is a consequence of the value clinicians and patients assign to the relative advantage offered by the new drug. In this sense, even though these calculations are conducted within a scientific framework, respondents expressed that there is still a certain degree of skill required to predict what the market will bear if the drug is the first of a new class.

I mean there is always this tension, because clearly ***we are for-profit companies, and for-profit within a health environment is quite…it immediately sets up some tension, particularly when you're working with public money****. So* ***all we can do*** *really is make sure that we* ***try to offer good value medicines****.* ***It doesn't mean cheap medicine it means medicines that are efficacious but are cost effective*** *(G1.1).*

It's also very ***important to design those studies*** *in a way where you* ***capture data for socio-economic, health economic cases that you can build for to understand the pricing of the medicine****. You know, that's* ***not just done by whim, it's done by a form of science. I mean it is an art****, and it's also a measure of the competitiveness of that field,* ***but if you're first in the market with a brand new medicine, with a brand new class, how do you price it?*** *You know, you've* ***got to find some means of demonstrating value of the brand and the product to the people who are going to pay for it*** *(CS1.3).*

I think it's something like 95% of drugs fail to make it to market, so there is always this ***tension between pricing, what the market can afford and what you need to be able to make a profit****, and also then you* ***have that across different markets****, first world, second world, third world, and so on, and* ***can you operate differential pricing,*** *which is clearly what we try to do to make it fairer,* ***without***

[23] The PPRS is a voluntary agreement between the Department of Health and the pharmaceutical industry that regulates the profits companies can make from NHS sales through profit caps and pricing controls.

it coming back to bite you*? So for example if you* ***supply drugs at cost in the third world, do you find them pitching up in the first world****? You know, so things like that, and* ***parallel imports*** *and so on and so forth (G1.1).*

Interview data suggested that prior to the establishment of formalised cost effectiveness systems, cost was often secondary to clinical considerations when prescribing decisions were more heavily influenced by clinicians, although this seemed dependent on disease area. The AA case demonstrated how the confidence one company had in the value offered by its drug was such that they priced it at almost double that of the first entrant with the insight that price was not paramount in psychiatrists' decision making.

In the BP case a price premium on the second entrant was thought to have caused slow adoption (although there were other factors at play in this case), until the benefits of a once weekly formulation were judged worthy of the increased cost. The emergence of formal health technology assessment through NICE and the increasing importance of non-clinical decision makers was seen as an influence on pricing strategy. Respondents indicated how pricing is now determined several years before launch with the assistance of payer advisory boards who guide pricing strategy according to whether a drug will be considered cost effective on its clinical profile, and approved by bodies such as NICE.

One of the reasons why olanzapine took off very quickly was that they actually came in and ***priced it at a higher price than Risperdal*** *(risperidone****) almost fifty percent as much****. Now* ***back then you could do that and it didn't create too much of an issue, so they priced high, they invested heavily in marketing activities, and that drove some very strong growth for them****. I think most of them would accept that Risperdal and olanzapine have a similar efficacy.* ***Psychiatrists are really not driven by price, even now, too much, it's the payers that have grown in influence,*** *but* ***back here*** *they had…- the* ***payers just had less of an influence and there wasn't as much cost pressure within the NHS****, there wasn't as much cost containment, and therefore, you know,* ***that growth was possible with the higher price*** *(CS2.1).*

They ***spent a lot of time trying to convince people that there was a significant benefit of the molecule, and they came at a price premium… and people did even understand that, even in the days before NICE*** *they understood that that's more expensive (CS1.1).*

I think it's ***up to three years you can talk about it, the purpose of advance notification is to notify payers if the new product is likely to have an impact upon their budget****, so that they can in the NHS financial cycle, they can build into their budget planning the expectation of the new product coming. So* ***you're allowed to share some basic information about what the product is, and what you would expect it to be priced at*** *(CS2.1).*

There are a number of ***payer advisory boards*** *as well, as in,* ***look at the clinical profile for this drug, look at the cost we're thinking of charging, do you think that it will get approved for use****? (G1.1).*

Respondents indicated how sharing pricing decisions with policy makers in advance was seen as a way of enabling planned market entry to avoid potential cost barriers to adoption. In a rapidly changing healthcare landscape however, whilst pricing is influenced by payers, respondents indicated the difficulties in anticipating and accommodating the needs of payers, particularly when those needs vary locally.

Then there's the ***payers, the PCTs****. Now, I mean this has* ***gone through so many evolutions in the last 15 years****, you know, you wonder where you are. I mean it's* ***becoming a very localised health economy*** *around the country, which* ***makes it quite difficult for us because it means we have to have multiple approaches depending on the locality*** *and that's down to the wrong distribution of resources, and that's an accent of history, the post code prescribing, you know, we know all the stories. But the* ***PCTs, you do need to present to them the cogent case of why this drug should be used, and today there is generally joint formularies between the secondary care setting and the PCT****, both agreed (CS1.3).*

I think the ***environment had changed****, the* ***NHS keeps evolving*** *so there are again, if anything,* ***by the time we launched that there were more checks and balances in place to slow down the acceptance of the drug****, so you know, NICE had just been invented… before we launched the product we had to do a* ***whole raft of work*** *on what I guess would now be called* ***access management to make sure that the non-prescribing elements*** *of the healthcare system are at least* ***aware, informed, understanding, and ideally from our point of view, accepting and positive about what we're doing*** *(CS1.2).*

Analysis of respondent views revealed that while first entrants face challenges in terms of price setting in the absence of a comparator, late entrants to a class are also confronted with difficult decisions regarding price due to the imminent risk of generics. Price was seen as a reflection of the competitiveness of a field. In a crowded market, for late entrants there become fewer points on which to differentiate relative advantage and so pricing effectively becomes the key differentiator.

***For some diseases it's much less of a barrier than others**. This [osteoporosis] there isn't a lot of choices, actually it's more important to me that the patient takes the drug. You know, so there's a **different motive that drives the prescribing behaviour**, and **price** still, they will **always think**, well, yes, there's not that many patients I treat, and actually it's **quite a small field, yes, I'll give these patients the best of, what I think is best for them**. **When you get into a massive field the price becomes hugely important** you know, like statins today is very different to what statins were 15 years ago (CS1.3).*

*If you've got products on the market which are more meaty, **some people will go for more of a pricing strategy, and so undercutting, and sort of commoditisation** (G1.2).*

Later entrants have the additional challenge of still needing to recoup development costs and maintain the value perception of adopters, so aiming at an anticipated generic price can be counterproductive. Respondents highlighted how the prominent role cost effectiveness analysis now plays has in some way diminished the significance of value perception amongst adopters in favour of lower acquisition costs where sufficient efficacy can be demonstrated.

*You look at **simvastatin now it's £1.59 for 40, as opposed to £18.05 or whatever ours is for ten. So even if we'd grown massively over two years we'd have still been hit now because of simvastatin 40** in the same way or to a lesser extent that atorvastatin has been hit (CS4.2).*

***The impact of simvastatin generic on the market at first was relatively modest** and the **price differential at first was not that great**… the Government was paying something like the original price of Zocor, so about £18 or £16. At that point, **we still had a cost effectiveness value in terms of the number of people brought to cholesterol target per pound**, so if people liked using atorvastatin they didn't immediately change their behaviour and say I can save a little bit of money by moving to generic simvastatin. The Government **got wise to that in May 2005 when they applied their category M tariff**. Category M was a new category where I think you could **pin the price to just one or two generic suppliers and it meant that the price dropped dramatically** (CS4.1).*

10.2. Price Perception

A quote from one of the respondents that "price is perception" exemplifies the importance of the psychology around pricing. The perception of the price of a drug at launch was considered by respondents as having a lasting effect on diffusion. While the price is used to reflect the relative advantage offered by the new drug, adopters' perception of price may also be influenced by the environment into which the new

drug is diffusing. For example, respondents discussed how if the comparator is already generic, as in the AAs, the class may be seen as 'expensive', whilst in the PDE5 inhibitor case anxiety about demand led to the belief that erectile dysfunction was going to be too expensive a condition to treat.

> *There was a **massive price difference between Risperdal (risperidone) and the conventional drugs**, because most of the conventional drugs…I think **all of them would have been off patent,** perhaps bar amisulpride, so there was a massive price difference, you know, probably talking **a tenfold price difference, so I think that would have constrained the growth as well to a certain degree** (CS2.1).*
>
> *It wasn't like this some sort of vague you know, notion of efficacy, it was; **worked in 70-80% of people on average, and it was safe, you know and to all intents and purposes and it wasn't expensive, it was £5 a tablet**, so that's £20 a month and that was absolutely in the **middle or the lower end of what most monthly medicine costs, so there was no reason to ban it, other than a fear about its uptake** (CS3.1).*

Pricing is also a fluid concept, with respondents highlighting how there is an opportunity to negotiate agreements with the Department of Health. While price is a product differentiator, by not being an innate feature of the drug, it is unlike other elements of relative advantage that are subject to a single opportunity at launch to be effectively communicated (see Theme 6: Communicating relative advantage; subtheme 6.1: Differentiating relative advantage). Respondents indicated that price perception based on comparisons can often be misleading therefore as the actual price may not be easily established due to issues such as complexities of dosing regimes or pricing structures in the NHS.

> *But **price tends to be perception which is created at launch**. **If they feel that it's expensive at launch it will always be expensive irrespective of whether it is or not** (CS1.3).*
>
> *It's **difficult to say what the price of etidronate really was**, **because of the cyclical nature of it**. So, it's kind of **awkward to do price comparisons**. It wasn't 'here's the daily price, here's the daily price' it was something like 'oh god it's too complicated' and **price is very much is perception for GPs**… for a drug which is primarily used in primary care they **don't see the real price anyway**, **they just see the list price** which is the NHS price which if they then **compare that with generics** or whatever, **you never know what the price of a generic is**, so it's **a highly flawed system**, but you know, it's probably good enough for the NHS (CS1.3).*

An interesting perspective discussed by respondents in the AA case was the concept that the setting of care in which a drug is prescribed may also impact on price perception. AAs limited to use in secondary care as a result of their route of administration, were considered to be under greater price scrutiny than those from the same class prescribed in primary care, despite being of equivalent or similar price. There was a belief that hospitals face greater price pressure on drugs than in primary care.

> *We are finding that **Risperdal Consta, although it's actually no more expensive than olanzapine, is being scrutinised for cost very heavily because it's paid for by the hospitals, whereas the other atypicals are paid for by the PCTs**, they're much more paid for by the PCTs, and with the **pressure on hospital budgets, we're finding that Risperdal Consta is coming under increasing scrutiny for cost, because hospitals have a much more constrained budget than PCTs** (CS2.1).*

Further into the lifecycle of Risperdal Consta, the fact that the molecule in its oral form came off patent (thereby increasing the differential) may have influenced this perception. Inevitably, the possibility arises that the new formulation will be plagued by comparison with the generic version in the minds of clinicians, even though the mode of administration tailors the drug to a potentially different patient group. Respondents indicated that in this scenario, it becomes a value judgement for prescribers as to whether the relative advantage offered by the new mode of administration outweighs the price difference.

> *I mean it really does mean that **you've got to show, you know, advantages over the generic product, because the cost difference is so great** (CS2.1).*

Analysis of respondents' views around pricing suggested they felt this factor can play a significant role in dictating the utility of the innovation i.e. while a new drug that responds to a genuine unmet need is less influenced by price, if the relative

advantage offered is not over and above current treatment, then a cheaper pricing strategy may be its only driver of diffusion. Aside from price issues, respondents had previously discussed how other factors were impacting on the way Risperdal Consta was being perceived by prescribers, particularly the negative associations of administering injections to patients with schizophrenia (see Theme 2: Clinician/patient experience; subtheme 2.2: Clinician-patient interaction).

5.4. Chapter comment

Thematic analysis of the interview data elucidated 10 major themes incorporating the factors respondents considered to be influential in the diffusion of pharmaceuticals, covering a range of social, economic and technological influences. These included: clinical need; clinician/patient experience; clinical evidence; health service/policy environments; adopter attitude; communicating relative advantage; market development; opinion leaders; company cultural heritage/perception and pricing. The validity of the findings and potential new insights contributed by the Industry respondents were revealed through triangulation with the other case specific data sources presented in the next chapter.

CHAPTER 6

TRIANGULATION OF CASE STUDY DATA SOURCES

6.1. Introduction

Triangulation compares the results from two or more data sources in the study of the same phenomenon. Triangulation can serve different functions depending on your philosophical position (either as a test of internal validity by providing a means of looking for patterns of convergence to develop or corroborate an overall interpretation (Yin, 1994; Mays and Pope, 2000), or as a means of completing the data by creating a richer picture of the phenomenon being researched (Stake, 1995)). The purpose of triangulation in this research was to ensure the data was complete through gathering multiple perspectives from a variety of sources, commensurate with a constructivist approach. With this perspective, points of convergence are not claims of truth, but instead provide the context for discussion of differences, which enhances completeness. Exploration of the divergent understandings then generates an enriched picture of the phenomenon.

6.2. Triangulation method

The three case specific data sources (diffusion curve; timelines and drug-specific Industry accounts) were cross-referenced to detect points of convergence and divergence between sources. As stated previously in Chapter 4, for confidentiality reasons it was not possible to present the individual drug-specific accounts, but they were integral to the thematic analysis. For the purpose of this chapter, a combined set

of factors derived from the accounts provided by Industry respondents for each case study has been presented in Figures 6.1 to 6.4 as part of a composite triangulation of data sources for the class.

6.3. Results

Overall, there was a high degree of convergence between the data sources to explain the shape of the diffusion curves. The Industry accounts however, elicited several insights that had not been revealed through the literature or expert consultations that in some cases could be supported by the diffusion curve trajectories. The points of divergence however, have to be considered as hypothetical explanations based on respondent views.

6.3.1. Bisphosphonates

The composite triangulation of data sources for the bisphosphonate case is presented in Figure 6.1.

Table 6.1: Bisphosphonates included in the triangulation analysis

Drug	Brand name	Manufacturer	Market hierarchy	Market entry position	UK launch
Alendronate	Fosamax	MSD	1	2nd	Sep 1995
Risedronate	Actonel	P&G	2	3rd	May 2000
Cyclical Etidronate	Didronel PMO	P&G	3	1st	Nov 1991

Points of Convergence – Why does the curve look the way it does?

Based on agreement between sources, the main themes of importance for this particular case study were:

- Disease perception – The Industry's challenge was to represent osteoporosis as a preventable disease. This took a long period of time due to traditionally held beliefs that osteoporosis was a feature of ageing, which could have accounted for the slow rate of diffusion of etidronate, compared with the eventual size of the osteoporotic population. Etidronate entered a premature market where disease awareness was minimal.

- Patient compliance with complex technologies – The various data sources support the concept that complicated administration protocols either due to irregular dosing, or to avoid tolerability issues led to patient discontent and non-compliance, which was supported by the slow diffusion of both cyclical etidronate and the daily formulation of alendronate, the course of which changed dramatically after the launch of the once weekly formulation.

- Adverse tolerability issues – Alendronate daily was plagued by adverse tolerability issues within the first year of launch, which was predominantly caused by a lack of adherence by patients to the complex administration protocol. The need for a 'dear doctor' letter in 1996 warning of potential safety concerns, was suggested as causing a marked slowing in alendronate's rate of adoption that continued until the introduction of a new formulation of the drug in 2001.

- Change in formulation – Demonstrating equivalent efficacy of a once weekly formulation of alendronate to its daily version was sufficient to revive its market potential. While it still required a complex administration protocol, the reduced frequency was considered by respondents to have been perceived by patients as less troublesome and also reduced the potential for adverse tolerability issues,

making it a more acceptable therapy. This shift was clearly visible on the diffusion curve, occurring at the same time point when the new formulation was launched in 2001.

- Evidence paradox – The Fracture Intervention Trial (FIT 1[24]), was expected to have a major impact on the uptake of alendronate. The study was of high quality and published in a prestigious journal in 1996, involved several thousand patients, was designed to report relevant clinical endpoints, and resulted in a favourable outcome for alendronate. It is not however, reflected in alendronate's diffusion curve post-publication in 1996, which coincides with the period when medical opinion had been potentially tainted by the emergence of safety concerns. Etidronate's curve shows small dips in use following publication of both the FIT 1 and FIT 2[25] studies, but it recovered on both occasions. The study that was attributed as having a substantial positive impact upon BP diffusion was the pharmacokinetic comparison that demonstrated equivalence between once daily and the new once weekly formulation of alendronate (Schnitzer *et al.*, 2000). While it was published in a lesser known journal, the results could be translated to the FIT 1 trial. Efficacy could be considered without the detrimental impact of the safety concerns associated with the daily formulation, enabling the FIT 1 data to take on its intended significance. The synchronous change seen in risedronate's diffusion curve following the launch of its once weekly formulation in 2003, exemplified the significance of 'ease of use' in the diffusion of pharmaceuticals, particularly for chronic diseases.

[24] FIT 1: Alendronate vs placebo 'megatrial' to demonstrate secondary prevention in vertebral and non-vertebral fractures. Published in December 1996.
[25] FIT 2: Alendronate vs placebo to demonstrate primary prevention of vertebral fracture. Published in December 1998.

- Guidelines/policy – Osteoporosis received significant attention between 1999 and 2001 in terms of the production of policy and clinical guidelines by several UK and international bodies. Their significance with regard to the shift that occurred in alendronate's curve in 2001 however is tenuous. As the guidelines did not distinguish between BPs, their effect would have been indiscriminate and a similar degree of positive impact would have been expected for risedronate at least, and this was not revealed by the curve data during that period. The timeliness of guideline publication defined the level of impact. Those produced early in the BP lifecycles, such as the WHO guidelines (1994) which helped to define osteoporosis, and the Royal College of Physician Guidelines on prevention and treatment (1999) were considered by respondents and the literature accounts as being instrumental in shaping clinical views, but this effect would have been gradual and therefore not identifiable through diffusion curves. When NICE guidance was published in 2005, at this late stage in the drug's lifecycle, it is likely that clinical practice was already established.

- Lack of competitor impact – The osteoporosis market was dominated by a relatively small number of players at the time of the interviews compared to some of the other case studies. The diffusion curves suggest that alendronate's introduction did not cause a sudden depression in etidronate's uptake and neither did the introduction of risedronate daily impact upon alendronate. Only when once weekly alendronate was launched did etidronate's use start to decline. The extent of this decline was not further accelerated by risedronate's weekly formulation however, potentially indicating preferential switching to alendronate weekly. Expectations that competition from major players outside of the BP class

(raloxifene and teriparatide) would result in market expansion for osteoporosis treatment and be detrimental to BPs is not supported by the curve data or the Industry accounts, which suggested raloxifene's minimal impact was attributable to reduced effectiveness in preventing hip fractures, while teriparatide was potentially too expensive for the UK market.

Points of Divergence – Industry specified factors

The following explanations were proposed by Industry respondents as explanations for the inflexions in the diffusion curves. These aspects were not elucidated through the background literature, and may or may not have been supported by curve.

- Expert consensus – Respondents explained how they felt there was a need to change attitudes towards disease perception before drugs for that condition could diffuse successfully, and that this was orchestrated through clinical opinion leader networks. Industry highlighted it was essential to gain an understanding of the hierarchy of influence in this field and establish the relationships necessary to reach a consensus view among clinicians on management strategies for the condition. The BP diffusion curves all show a slow rate of initial adoption that could reflect the culture of clinicians in this disease area. It could also reflect the impact of the postulated access barriers to specialists resulting from respondents' belief that GPs were reluctant to manage the condition in primary care.

- KOL loyalty – Evolution of opinion leadership from within one company as a result of the novelty that surrounded disease classification was believed to have detrimentally impacted on competitors that later entered the field. Opinion

leadership loyalty was perceived as a marker of allegiance to the company who had built and established the market, but as a barrier by competitors. The diffusion curves could support this view by showing 1) an unexpectedly slow period of adoption for alendronate post-launch in view of the evidence suite and marketing efforts, and 2) the fact that there was not a rapid decline in the use of etidronate considering the substantial difference in efficacy. P&G also stated that they had not mounted a response towards the market entry of alendronate in the knowledge that its second drug risedronate was due to enter the market soon after. KOL effect is however, impossible to dissociate from the impact of the safety issues or the increased cost of alendronate that would have affected the extent of relative advantage offered by its increased efficacy. With the advent of once weekly alendronate, respondents considered it would have been very difficult for opinion leadership loyalty to have continued for etidronate as it would have risked credibility to support a significantly less efficacious drug when tolerability was no longer a barrier. The diffusion curve could support this view as etidronate use only started to decline substantially when the once weekly formulation of alendronate entered the market, but this was also largely believed to have been driven by patient preference for the new formulation.

- Culturally influenced approach to market entry – Respondents believed that adopting a mindset influenced by a heritage of successful practices in other disease areas did not translate well to osteoporosis. They believed it resulted in focusing attention on the wrong opinion leaders (primary as opposed to secondary care where they eventually believed the influence lay). The emerging nature of the osteoporosis field, coupled with the suggestion that the key opinion

leaders were closely associated with the first company to produce BPs may have created an environment where it was difficult for competitors to fully comprehend and foster the relationships necessary to achieve opinion leadership support. This view could be supported by the relatively slow rate of uptake experienced by alendronate, but there were many other confounding factors operating at that time.

- Journal control – The restrictions imposed by a high impact factor journal in the way findings from a key study (McClung *et al*., 2001: risedronate vs placebo), were communicated (i.e. no pre-release of results and full explanations for inconsistencies in trial outcomes) was considered by respondents as a possible factor responsible for compromising the uptake of risedronate. The delay in publication was felt to reduce the impact of the data compared with gradual release that may have maintained interest, and secondly they felt the overall simplicity of the message became complicated by caveats. The trial appeared to make little positive impact on risedronate's diffusion curve or a negative one on its main competitor alendronate. Its timing however, coincided with the launch of the once weekly formulation of alendronate, which could also account for its limited impact and alendronate had fortuitously proved several years earlier the outcome the risedronate trial was designed to demonstrate.

- Obsolescence of daily preparations - Risedronate 'daily' – Despite not having the same degree of tolerability issues, risedronate daily was plagued by association with the problems experienced by daily alendronate. The favourable reception by patients and clinicians to 'once weekly' alendronate, introduced only a few months after daily risedronate, set a new benchmark that was perceived to have

limited any further growth in daily preparations. Respondents felt that expectations had moved on, making daily preparations obsolete.

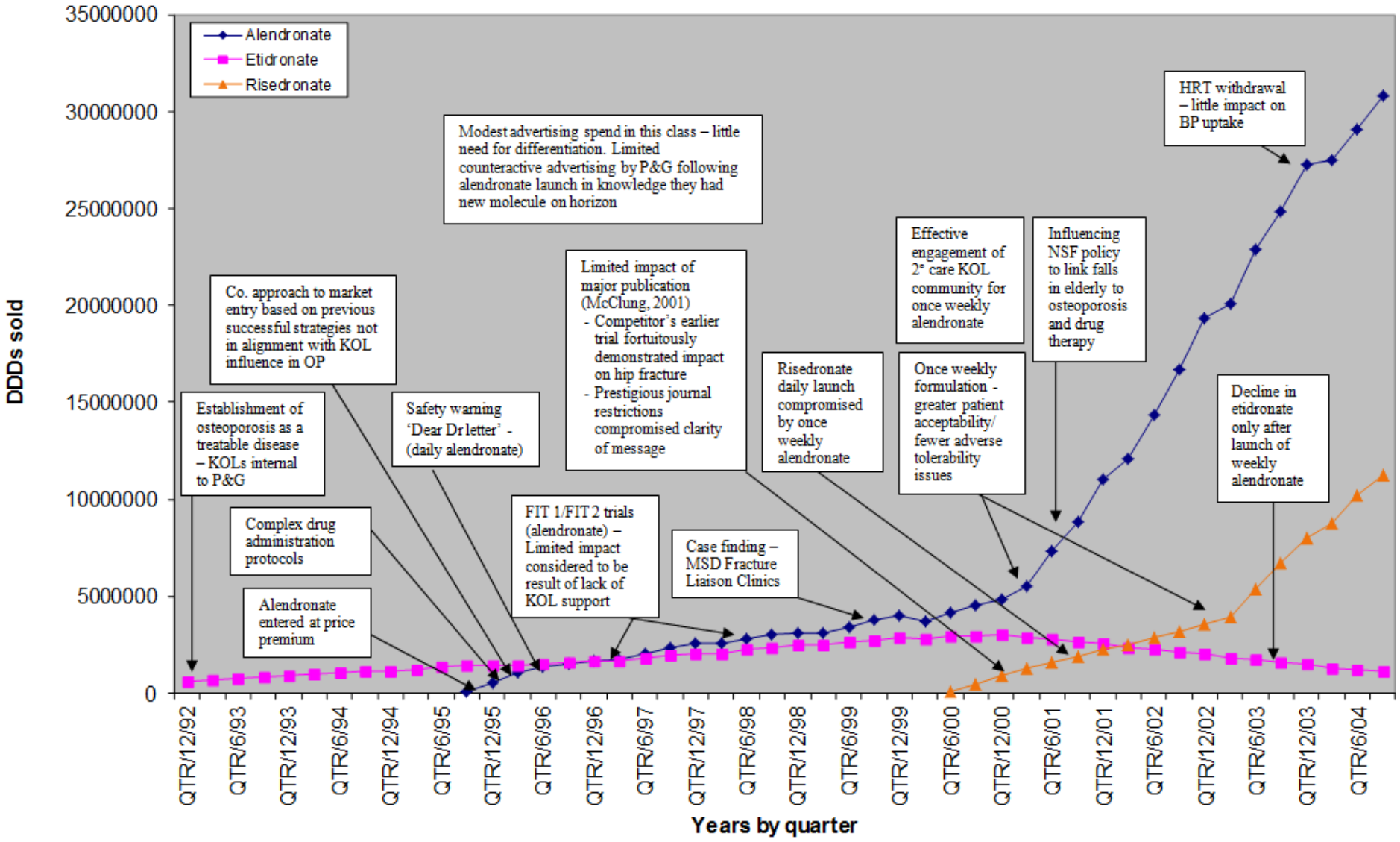
- Market leader activities – Respondents considered that market leadership activities that helped to increase diagnosis of osteoporosis were important in expanding the market for BPs. It is difficult to separate the effect of market expansion efforts to identifiable phases of the diffusion curve as the impact would have been cumulative over a long period. Alendronate overtook etidronate marginally around mid-1997, but the trajectories of the two drugs did not diverge significantly for a further three years. A slight increase in use of alendronate was evident at the time MSD introduced Fracture Liaison Clinics. The tolerability profile of alendonate however, was likely to be a limiting factor to a marked increase in alendronate prescribing despite possible increased rates of diagnosis. P&G however, also did not appear to gain market share from any of the potential activities MSD were involved in to expand the eligible patient population. It did perhaps set the foundations for alendronate's rapid expansion in use when tolerability was no longer a barrier with release of the weekly preparation. Activities taking place outside of the pharmaceutical market, such as mergers between diagnostic companies with interests in osteoporosis were highlighted as potentially having provided additional resources to raise the profile of the condition.

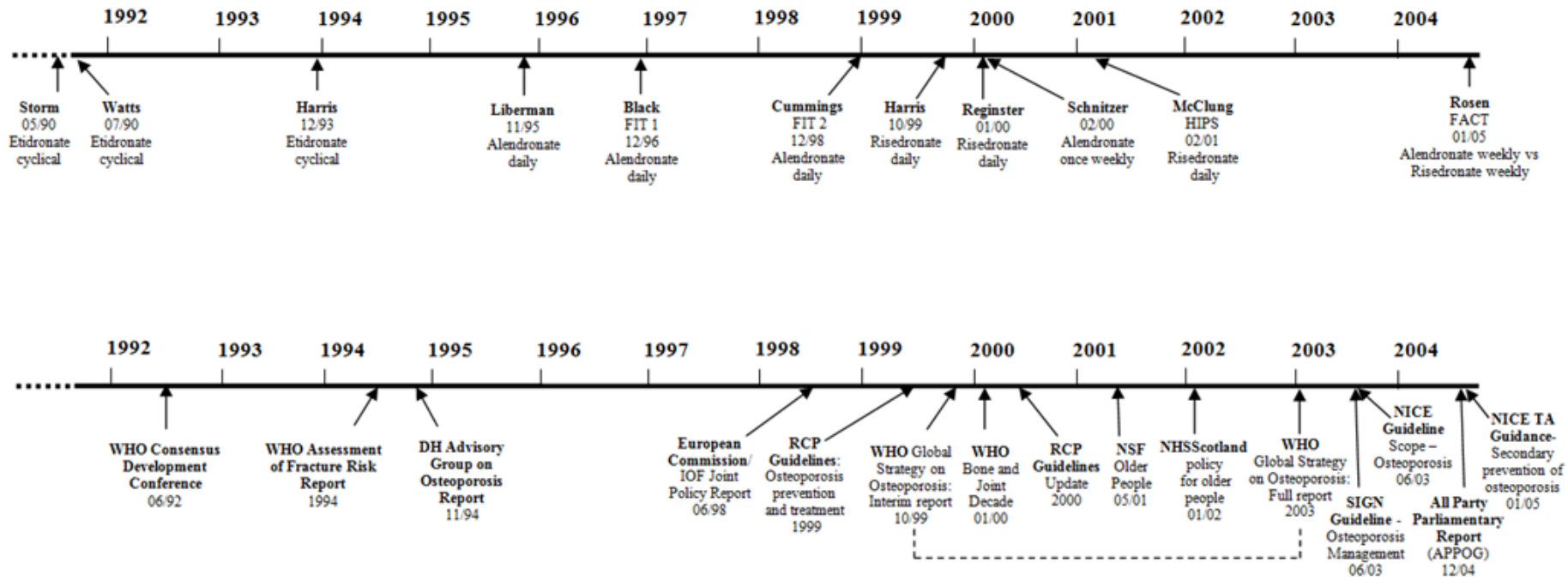
- Partnerships – Partnering with Hoechst Marion Roussel (a traditional pharmaceutical company) in the early stages of risedronate's development was considered by respondents as being important to diffusion as a it provided pharmaceutical marketing expertise that P&G had initially lacked with etidronate

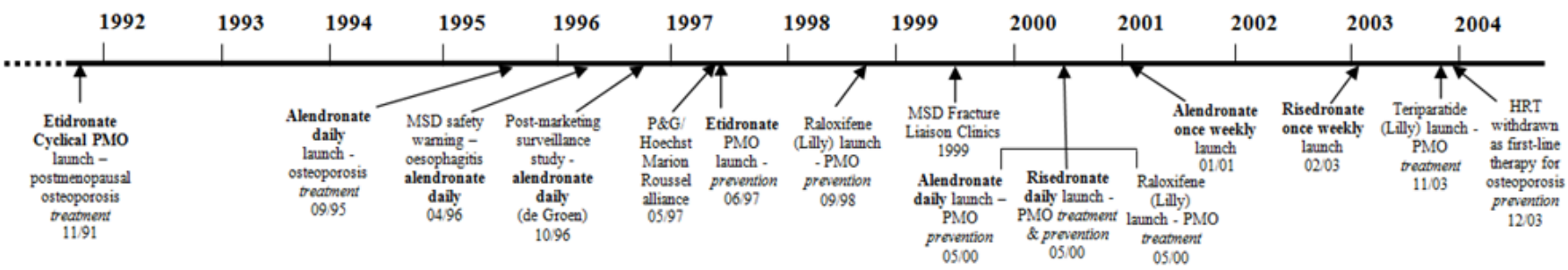
as a consequence of its consumer-based heritage. The rate of uptake was greater for risedronate daily compared with etidronate, but the osteoporosis market had become established by this point and the arrival to the market of once weekly alendronate so soon after its launch would have been likely to hamper any additional marketing impact provided by Hoechst Marion Roussel for risedronate daily.

- HRT withdrawal – Withdrawal of HRT towards the end of 2001 was not considered by respondents as a driver in the osteoporosis market, which disagrees with views expressed in the literature. As BPs were not licensed for this indication, respondents explained it was not something they could promote. The diffusion curve is supportive of the Industry perspective in that the curves for alendronate and risedronate continued on at the same angle of upward trajectory in the months that followed the withdrawal of HRT, as opposed to showing any dramatic increase in use. Alternatively, the slight plateau visible in alendronate's curve at this point, while potentially a data artifact could have indicated the start of the saturation phase. HRT patients may then have opened up a new potential market for continued diffusion.

Figure 6.1: Bisphosphonates - Composite Triangulation







6.3.2. Atypical Antipsychotics

The composite triangulation of data sources for the atypical antipsychotics case is presented in Figure 6.2.

Table 6.2: Atypical antipsychotics included in the triangulation analysis

Drug	Brand name	Manufacturer	Market hierarchy	Market entry position	UK launch
Olanzapine	Zyprexa	Eli Lilly (now Lilly)	1	5th	Oct 1996
Risperidone	Risperdal	Janssen-Cilag, Organon	2	3rd	Jun 1993
Quetiapine	Seroquel	AstraZeneca	4	6th	Sep 1997

Points of Convergence – Why does the curve look the way it does?

Based on agreement between sources, the main themes of importance for this particular case study were:

- Clinical need – Unprecedented latent unmet clinical need from clinicians in a field of medicine that had not seen any new drugs for several decades was recognised as creating the degree of anticipation for a new innovation. 'Clinical need' on its own however, was insufficient to ensure successful diffusion, otherwise risperidone would have benefitted maximally from the demand. The diffusion curve data demonstrated that the next entrant, olanzapine benefitted most from clinicians' anticipation for a new treatment shown by a rapid rate of adoption.

- Ease of use – Olanzapine was able to meet the additional clinical need in this disease area of 'ease of use'. While risperidone had entered the market not requiring the same level of monitoring as clozapine, titration was still necessary to

obtain the optimal dose. Olanzapine however, offered a single dosing strategy that appealed to psychiatrists and enabled it to benefit maximally from the unprecedented level of clinical need.

- Safety warnings/issues – On a simplistic level the AA curves can be divided into two sections; the acceleration phase and the plateau phase from 2004 onwards. The start of the plateau phase was attributed to the Committee for the Safety of Medicines letter warning against the use of risperidone and olanzapine for the unlicensed treatment of behavioural disturbances in elderly patients with dementia due to the risk of cerebrovascular adverse events. This had an immediate effect on the diffusion of these two drugs shown by the mirrored decline in the trajectories of their curves from March 2004. Concerns regarding metabolic issues did not appear to affect the diffusion curves initially, but contributed to the growing apprehension during the later phases when their effectiveness against conventional antipsychotics started to come under question. To lessen the impact of the latter stage decline, an Industry priority was to gain recognition that weight issues were a physiological symptom of schizophrenia so that services to manage physical health could be implemented.

- Pricing barrier – Despite anticipation of a new drug, the relatively slow uptake rate of risperidone was attributed to the price differential compared with generic conventional antipsychotics. Olanzapine's comparator however, was branded risperidone, which reduced the impact of price on uptake. In this case it was beneficial to enter the market once the class properties had been established.

- Evidence – There were no obvious inflexions in the diffusion curves that could be attributed to the publication of the early pivotal studies in 1997 (Tollefson *et al.*, 1997: olanzapine vs haloperidol and Tran *et al.,* 1997: olanzapine vs risperidone). Respondents were of the view that these trials effectively became redundant as psychiatrists had already formed their own opinions based on personal experience with the drugs. The studies were therefore felt to be confirmatory. The impact of the trial by Csernansky *et al*. (2002) on risperidone is difficult to determine as there was an increase in the curve trajectories of both risperidone and olanzapine during that period. At this point the environment was confounded by several other factors, such as the release of the long-acting formulation of risperidone, and olanzapine's bipolar indication, which could have accounted for the increase and disguised the trial impact. In the later phases, the large-scale publicly funded trials (CATIE (2005) and CUtLASS (2006)) that indicated no significant differences between conventional and atypical antipsychotics, together with the mounting concerns of side effects appear to have slowed diffusion, although the Industry did present alternative explanations for diffusion barriers in this period (see following section).

- Competitors – The entrance of competitor molecules could be seen to impact on the trajectories of those already available. The launch of olanzapine depressed the uptake rate of risperidone, and entry of quetiapine to the market did affect the trajectories of both risperidone and olanzapine, although not to a great extent.

- Guidelines/policy – There were a series of guidelines and policy documents produced between 1999 and 2000 that correspond with the initial expansion phase of the AA market. Both the NSF for Mental Health and the Maudsley

Guidelines produced during 1999 were attributed to bringing attention to the disease area. Their importance was corroborated by respondents as they led to reconfiguration of services and standards, and corresponded with a marked change in the trajectory of olanzapine and risperidone (but only marginally for quetiapine), despite the presence of safety concerns that existed following the withdrawal of the AA sertindole. The impact of NICE guidance and guidelines in 2002 however, whilst consistent with increases in the curves of all three AAs indicating a class effect, was not perceived by respondents to have had a major impact. They were produced at around the same time when several other events were occurring regarding new indications and off-label usage (see below), therefore their individual contributions are difficult to assess. A meta-analyses indicating no clear advantages of AAs over CAs ahead of the CATIE and CUtLASS trials produced in 2000 did not appear to have impacted on the AA curve trajectories suggesting evidence was not necessarily a key influential factor governing decisions in this disease area.

Points of Divergence – Industry specified factors

- Off-label usage – The upward trajectories mirrored in the diffusion curves of both risperdone and olanzapine during 2001 were attributed by respondents to switching of elderly patients with dementia from a drug (Melleril) that had received a Committee for the Safety of Medicines (CSM) warning in December 2000, to AAs despite this class of drugs not being licensed for this indication.

- Communication impacting on clinician experience – Clinician experience was not necessarily a factor in why the second entrant became the market leader, but it

was considered as being instrumental in preventing the other two drugs from reaching their potential diffusion capabilities. Both risperidone and quetiapine were affected by confused dose messages at launch that were believed to have impacted upon clinicians' perceptions of their efficacy. It was claimed that risperidone was used at too high a dose initially and did not achieve the desired separation from the conventional antipsychotics it was competing against. Similarly, quetiapine was believed to have been affected by use of too low a dose and so did not demonstrate equivalent efficacy to the other AAs (in attempts to change perceptions, respondents described how NICE guidance, which did not differentiate between AAs, was used to support a message of equivalence for quetiapine). It is not unusual for the UK to be conservative in its adoption of new medical technologies (Wanless, 2002), but the fact olanzapine was not affected by a slow rate of adoption could support the notion that inappropriate use leading to a lack of clear effect may explain why the UK was the slowest of the major economies to adopt some of the atypical antipsychotics despite the plethora of published data (Geddes, 2003). The dosing message was clarified for the launch of quetiapine's bipolar indication, which corresponded to an increased trajectory in its diffusion curve from 2004.

- Market positioning – Quetiapine was initially positioned against its competitors on the basis of an improved side effect profile rather than on efficacy grounds (i.e. equivalent efficacy to existing drugs, but with fewer side effects) based on market research that had indicated that side effects were the pertinent issue in psychiatrists' prescribing decisions. Efficacy was however found to be important in practice. This required a change in strategy to alter psychiatrists' perception of

efficacy from a short to a longer-term concept. This achieved differentiation as patients tended to fare worse over time with the other AAs. The nature of the condition however, was such that respondents believed that management of acute manifestations is at the forefront of psychiatrists' minds rather than focusing on the longer-term issues, as their strategies to change this perspective had little impact on accelerating diffusion.

- Sales force presence – In conjunction with specific pricing and communication issues, the initial slow uptake rates of risperidone and quetiapine were attributed to limited sales force investment. In the periods where sales force presence was increased, either as a consequence of mergers, or through re-evaluation of market potential within the company's portfolio, the trajectory of the curves increased steadily in the period between 1999 and 2003, but without any obvious inflexions in these time periods.

- New formulations – The Industry believed that additional new formulations such as soluble, and short- and long-acting intramuscular preparations, were justified as they were responding to identified clinical needs. This was supported in their view by steeper gradients in the diffusion curves following the launch of these formulations. Respondent insights suggested however, that continued adoption of intramuscular Risperdal Consta was hampered by irrational perceptions held by prescribers towards injection preparations derived from association with injectable preparations for other management scenarios in schizophrenia (acute sedation of manic patients). This was occurring however, in an environment

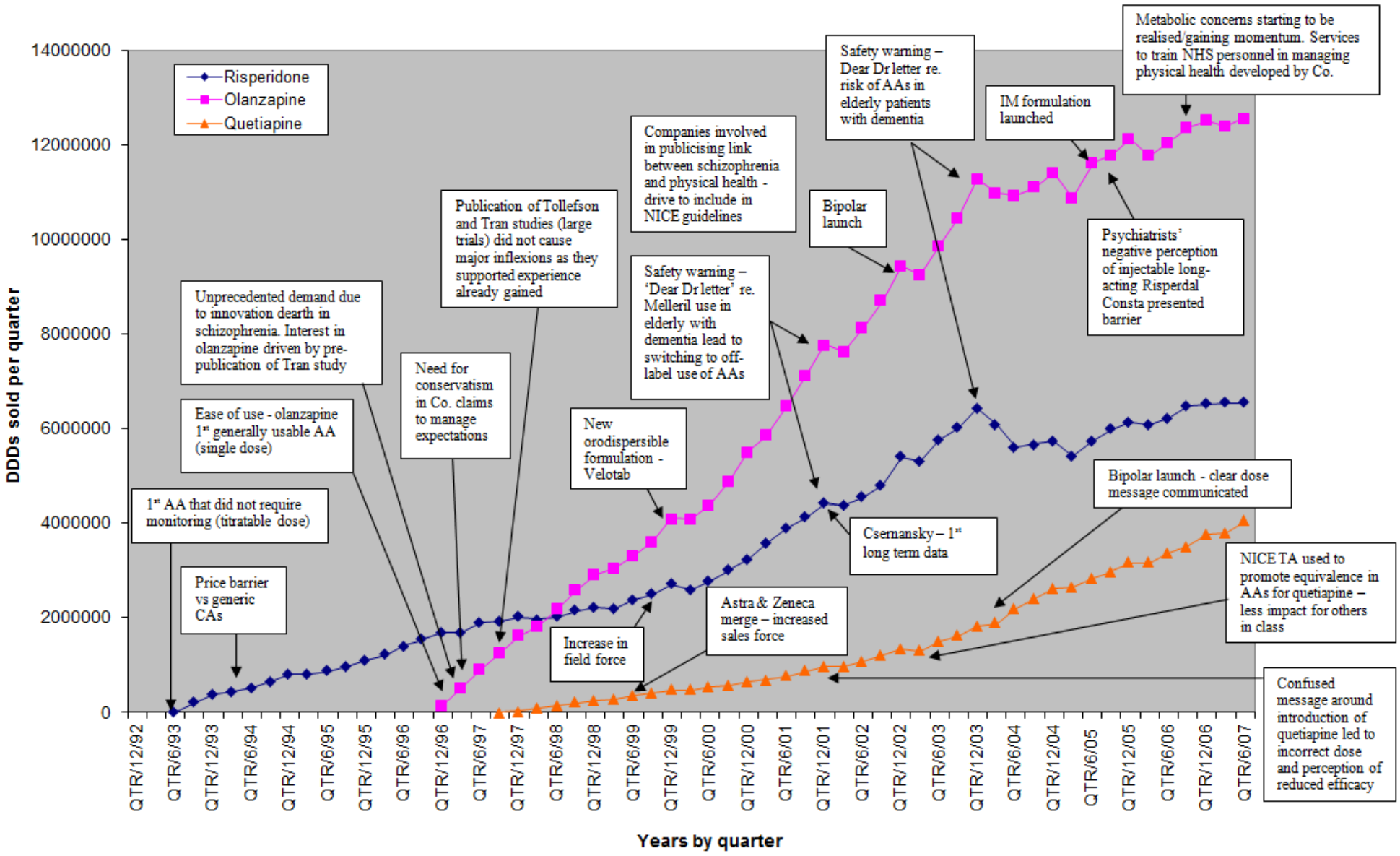
where clinical trials were also demonstrating little or no difference between conventional and atypical antipsychotics.

- New indications – The increase in the gradient of olanzapine's curve between 2002 and 2003 was suggested by respondents to be due to the new bipolar indication. While olanzapine was the first AA to obtain this additional indication, similar rates of increase were not observed with the other AAs when they obtained their bipolar indications.

- Limited role of advertising – Respondents considered the purpose of advertising is to create awareness, but in circumstances where awareness is already high ahead of launch, due to adopter interest or through early release of trial results, their view was that advertising was not influential in these circumstances.

- Clinical setting – Prescribing of all AAs was limited by the professional barrier presented by the reticence of primary care to manage patients outside of specialist guidance.

Figure 6.2: Atypical antipsychotics - Composite Triangulation



6.3.3. PDE5 Inhibitors

The composite triangulation of data sources for the PDE5 inhibitor case is presented in Figure 6.3.

Table 6.3: PDE5 inhibitors included in the triangulation analysis

Drug	Brand name	Manufacturer	Market hierarchy	Market entry position	UK launch
Sildenafil citrate	Viagra	Pfizer	1	1st	Sep 1998
Tadalafil	Cialis	Lilly	2	2nd	Feb 2003
Vardenafil hydrochloride	Levitra	Bayer	3	3rd	Mar 2003

Points of Convergence – Why does the curve look the way it does?

Based on agreement between sources, the main themes of importance for this particular case study were:

- Unmet clinical need – Existing treatments for ED were of low patient acceptability mainly due to their modes of administration. This resulted in a significantly under-treated population and the need for a new type of therapy. This perspective was supported by the high level of interest in the subject just prior to the release of sildenafil.

- Oral mode of administration – The offering of an oral formulation appealed to patients, such that the potential scale of the ED market started to become realised as interest grew not only amongst clinicians, but also from patients. This market anticipation was driven by extensive media coverage following the USA launch of sildenafil that took place a few months ahead of the UK launch.

- Government policy – An unprecedented decision was taken by the Government immediately before the UK launch of sildenafil to effectively ban the

prescription of the drug on the NHS based on fears of excessive demand (by implementing this government policy it was a clear acknowledgement of the need for NHS rationing). The steep gradient of sildenafil's diffusion curve, however demonstrated that the drug continued to be prescribed, which was attributed to defiance of the ban initially by some clinicians following legal advice sought by the BMA indicated the guidance to be unlawful. The reduction in the rate of uptake by September 1999 reflects the period immediately following when the prescribing restrictions, while lessened to include certain patients groups, became law. The change in the angle of trajectory of sildenafil's diffusion curve at this point suggests how the diffusion ceiling of the drug was significantly curtailed by the prescribing restrictions.

- Media attention – The media attention brought a condition that was largely hidden from public discussion to the forefront of public interest. This was partly fuelled by misconceptions that sildenafil could be used as a drug of abuse to enhance rather than normalise function. The rapid uptake rate demonstrated in the initial phase of the diffusion curve could support the impact of the media in diffusion as it was key to raising awareness that encouraged patients to seek treatment.

- Clinician autonomy – The belief that the autonomy of clinicians was being challenged by the Government's ban was considered to be the reason that led the British Medical Association to encourage its members to continue prescribing sildenafil until the restrictions were given the rule of law. This allowed diffusion to take place in the period between launch and when the restrictions became lawfully enforceable under Schedule 2 in May 1999. One of the conditions for

which it was still possible to prescribe sildenafil on the NHS (men suffering severe distress on account of their ED) was considered by respondents and the literature to be broadly interpreted by clinicians, such that diffusion continued in this constrained prescribing environment, albeit to a reduced capacity to that originally anticipated.

- Disease perception – Overcoming the embarrassment and stigma surrounding this condition was partly achieved through medicalisation (shift in terminology from impotence to ED). ED, which was a pre-existing term, changed the emphasis from it being perceived, particularly by patients, as a psychological condition to that of one with an organic cause. The impact was to alter clinician perception of ED from a lifestyle condition to that of a serious, yet treatable condition. The diffusion curve can only reflect the impact of this change through its increasing gradient in the post-launch period.

- Competitor challenge – The almost simultaneous launch of two competitors within one month of each other caused an obvious reduction in the gradient of sildenafil's diffusion curve. Tadalafil's longer period of action however, was a clear point of differentiation that responded to patient need, reflected by the larger percentage of market share it was able to obtain compared with vardenfil, which was unable to achieve sufficient differentiation from sildenafil. A different approach to marketing was seen as being necessary to differentiate tadalafil from sildenafil.

- Widening access – The peak in sildenafil's diffusion curve seen at the beginning of 2007 was as a result of a Patient Group Direction that enabled access to

sildenafil through pharmacies, and caused a momentary reduction in tadalafil prescriptions.

- Evidence – With the exception of the pivotal studies that heralded their introduction, trials did not appear to be a major driver in decision making in the diffusion of this class, despite the vast amounts of data generated by them. As efficacy of the drugs for this condition is tangible, preference is highly patient-driven, according to the characteristics afforded by the different drugs in this class. The brief decline in the gradient of sildenafil's curve and the slight increase in that of tadalafil's at the beginning of 2006 may have reflected the impact of preference studies that favoured tadalafil. However, as the diffusion of sildenafil was not significantly affected in the period that followed, this could suggest that the increased usage of tadalafil may be more reflective of market expansion activities.

Points of Divergence – Industry specified factors

As most points of divergence were based on social factors, it is difficult to attribute inflexions on the diffusion curves to them, and instead they are more likely to be represented as gradual positive and negative inclines.

- Incompatibility of clinician/patient needs – The incompatibility between clinician priorities (restoration of function) and patient needs (restoration of intimacy) was perceived by respondents as having prevented clear communication during consultations of the relative advantage that a long-acting drug could provide. The choice given to patients included a long-acting drug, but the implications that

characteristic afforded i.e. the potential for spontaneity was thought by respondents as not being adequately explored during consultations. The initial uptake rate of tadalafil was similar to sildenafil, but this lack of discussion could have contributed to the reduced rate of subsequent adoption witnessed after the first year.

- Primary and secondary care boundaries – The intended shift of ED management from urology to primary care made possible by the oral mode of administration was curtailed by restrictive government prescribing policy. Respondents discussed how this transferred prescribing policy back to secondary care specialists as the conduit through which treatment could be obtained, but their limited numbers presented a barrier to access compared to what would have been possible through primary care.

- Opinion leader involvement – Respondents believed that sensitive management of opinion leaders in secondary care was crucial in getting an oral drug that was going to be predominantly managed in primary care accepted by them, so as not to undermine the influence of specialists and get them on board.

- Evidence barrier – Extensive clinical trial programmes were effectively used to block competition by raising the benchmark of the evidence suite necessary to compete on a level playing field. This was perceived by respondents as having presented a cost barrier for competitors.

- Sales force dynamics – Withdrawal of a co-marketing partner in the case of vardenafil resulted in a reduction in sales force presence. While its impact was not

immediately represented in the diffusion curve, the subsequent use of a contract sales force that did not possess the same level of established trust with clinicians as GSK representatives held, was thought by respondents to have contributed to limiting the rate of its adoption.

- Influence of secondary care – One company's strategy to scale back secondary care representatives to focus entirely on primary care was suggested by respondents as being the cause of a curve plateau. Despite the vast majority of prescriptions being maintained in primary care, respondents believed that specialists continued to retain prescribing influence.

- Counterfeit impact – The view from respondents was that the presence of counterfeit versions of the molecule and the ability to purchase these drugs online has been responsible for severely compromising the potential ceiling of the diffusion curve for drugs in this class.

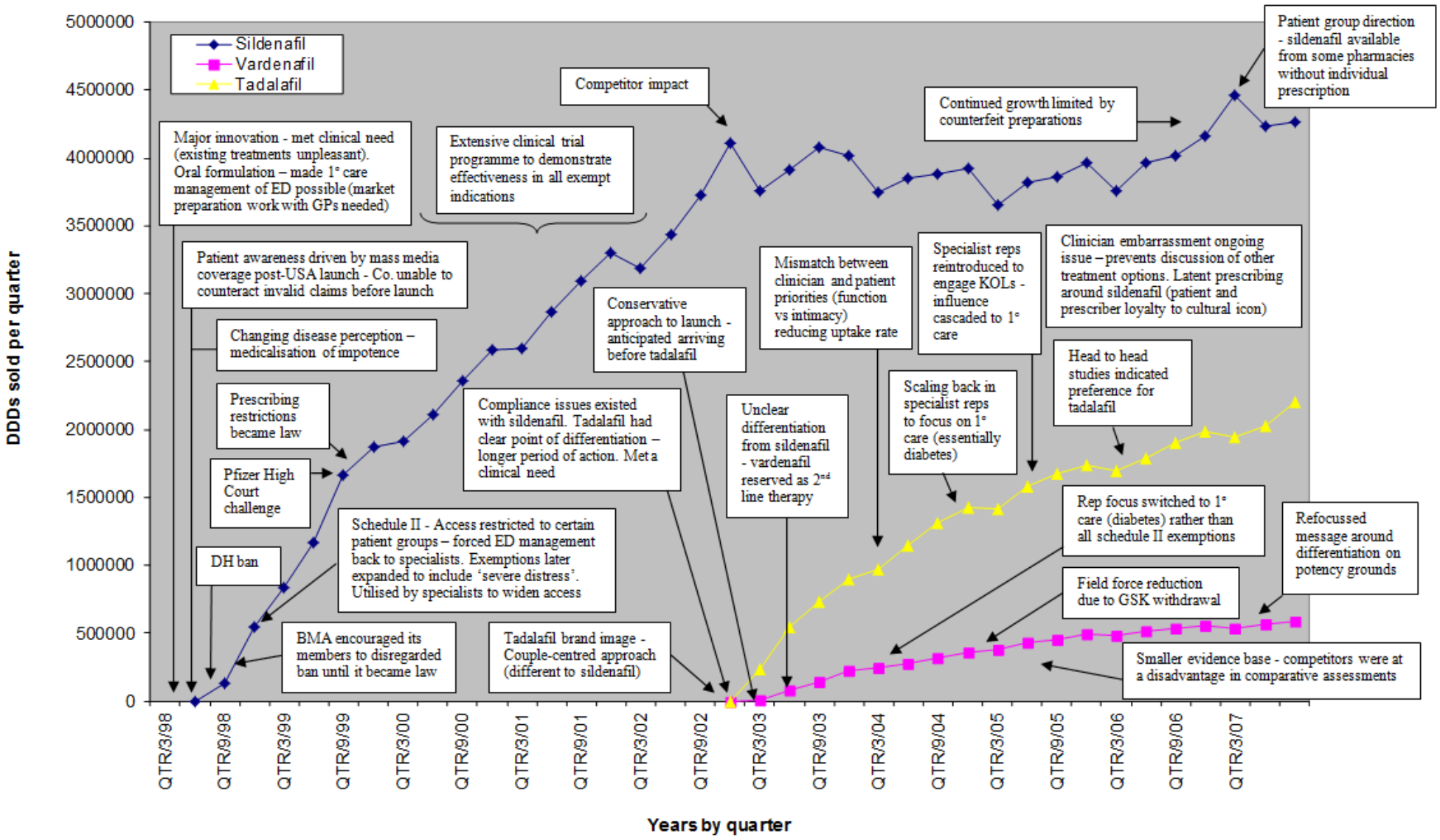
- Policy impacting on compliance – The use of policy to ration availability of PDE5 inhibitors to one tablet per week was believed by respondents to impose artificial conditions on what ideally is a spontaneous act. The impact, in their view, was that it often disengaged patients from wanting to continue with further treatment. Discontinuation rates of PDE5 inhibitors are relatively high, therefore the market research insights that respondents have on this matter could present this as a plausible explanation.

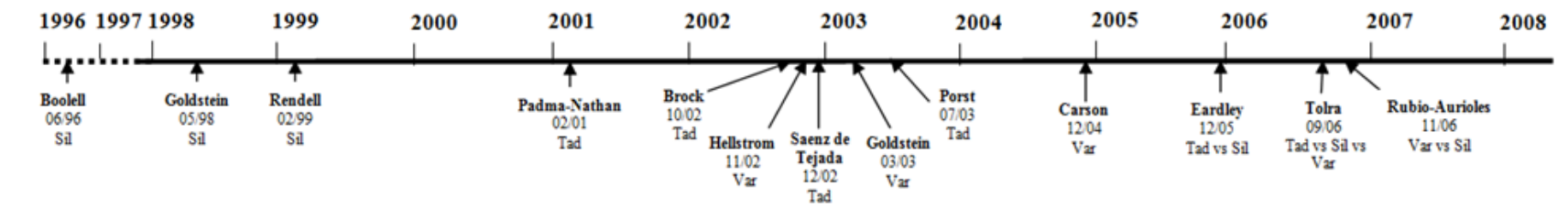
- Clinician embarrassment – Embarrassment experienced by clinicians and patients was thought to be the cause of reticence to fully discuss alternative treatment options with patients. Embarrassment was also believed to be a factor in why

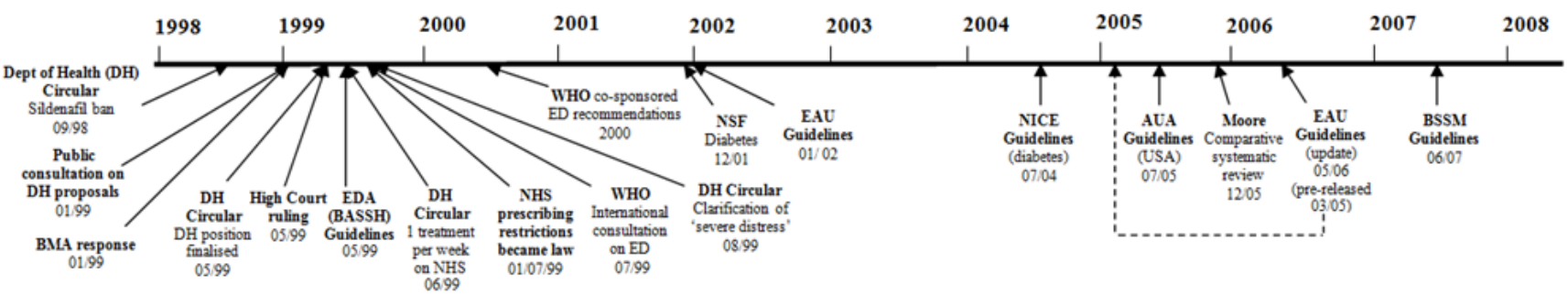
there had been poor implementation of NSF policy objectives around ED. Sildenafil was thought to benefit from this issue as respondents perceived that patients requesting a particular brand were not generally dissuaded with a full discussion of the advantages and disadvantage of all other possible options.

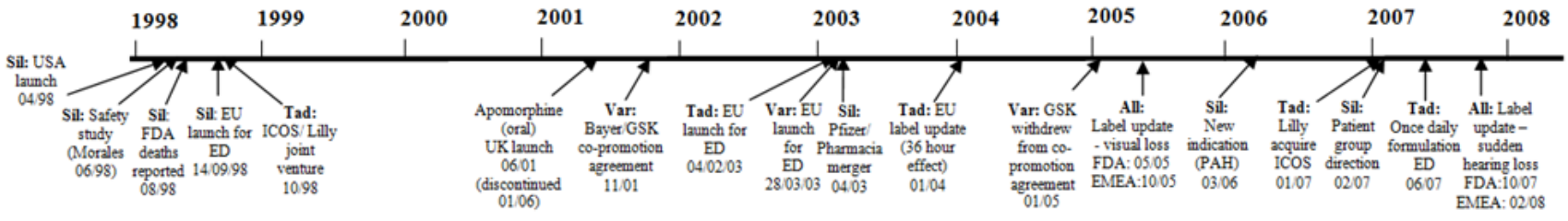
- Drug perception – The failure to adequately differentiate vardenafil from sildenafil was thought to be the reason why vardenafil became reserved as a second-line treatment. Vardenafil was also likely to fail in sildenafil resistant patients, which was believed by respondents to have reinforced clinicians' negative perceptions of the drug's efficacy.

Figure 6.3: PDE5 inhibitors – Composite Triangulation









6.3.4. Statins

The composite triangulation of data sources for the statin case is presented in Figure 6.4.

Table 6.3: Statins included in the triangulation analysis

Drug	Brand name	Manufacturer	Market hierarchy	Market entry position[26]	UK launch
Atorvastatin	Lipitor	Pfizer	2	4th	Mar 1997
Rosuvastatin	Crestor	AstraZeneca	4	6th	Mar 2000

Points of Convergence – Why does the curve look the way it does?

Based on agreement between sources, the main themes of importance for this particular case study were:

- Evidence – The landmark 4S mega-trial in 1994 (simvastatin vs placebo) initiated the rapid uptake of statins (simvastatin had already been on the market for five years at the point of publication). The trial was sufficiently powered to prove that LDL-C reduction not only reduced cardiovascular mortality, but also total mortality through secondary prevention of cardiovascular events. It was this feature that was necessary to tip the balance in changing clinical practice. While the impact seems minimal on the scale of the eventual diffusion curve, there was a significant change in its trajectory following publication of the study (see Figure 4.7 for an expanded view of the initial diffusion period). WOSCOPS (pravastatin vs placebo), published in 1995, which quickly followed publication of 4S, opened up an additional market. It demonstrated effectiveness of statins in

[26] Lovastatin was the first statin but it was not launched in the UK. Interviewees often discussed worldwide market entry position, making atorvastatin the 5th and rosuvastatin the 7th statin.

primary prevention, which presented a significantly larger eligible patient population.

The late 1990s, and into the mid-2000s was a trial active period (atorvastatin and simvastatin diffused in parallel[27]). The largest of these was the independently funded Heart Protection Study (2002) (simvastatin vs placebo), which was key to supporting continued use of simvastatin (on the grounds of proven clinical outcome efficacy and safety) in amongst a dominating series of atorvastatin mega-trials (see Appendix 16 for further details of trials).

- Clinical scepticism – Before the 4S study, the views of respondents and the literature supported the belief that the medical community was unconvinced of the benefits of LDL-C lowering, despite evidence demonstrating a reduction in cardiovascular mortality. The barrier to statin adoption at that time was justified on the basis of questionable efficacy. Then despite demonstration of efficacy through the 4S trial, scepticism still persisted, but manifested in concerns over safety of the class (rhabdomyolysis and increased mortality associated with persistently low LDL-C levels). This contributed to the relatively low level of diffusion in the period post-4S compared with what was eventually achieved by this class. The lack of early opinion leader support for the LDL-lowering concept was a barrier to adoption for statins.

- Relative advantage – Ease of use afforded by atorvastatin offered a relative advantage that appealed to prescribers. The lack of clinical outcome studies at its

[27] Pravastatin was a viable competitor to the major statins, simvastatin and atorvastatin initially, but the null outcome of the ALLHAT trial of pravastatin against usual care was responsible for its truncated diffusion, despite numerous earlier positive trials (e.g. WOSCOPS, CARE and LIPID) .

launch did not appear to present a barrier as confidence in the statin effect was such that extrapolations to clinical impact were being made on the basis of atorvastatin's greater potency on surrogate markers. As a 4th entrant, atorvastatin gained almost equivalent market share to simvastatin within three years of launch and remained on a par with simvastatin for a period even after generic simvastatin became available. Rosuvastatin had greater potency, but safety concerns limited the impact of this benefit.

- Policy – The identification of cholesterol lowering as a government priority in the National Service Framework for Coronary Heart Disease (CHD) in 2000 appears to have been a key factor in boosting statin usage. This was further enhanced by inclusion of cholesterol targets in the QOF in April 2004 that incentivised the prescribing of statins. This was supported by the continued steep upward trajectory across all statins (evident on rosuvastatin's individual curve, but masked by scale on the group charts).

- Safety – Despite launching into a cautious market tainted by the withdrawal of cerevastatin and the prospect of simvastatin becoming generic within a few months of launch, rosuvastatin experienced rapid adoption. However two safety warnings issued in quick succession for rosuvastatin in mid-2004 soon after its launch (due to incorrect use of starting doses higher than recommended) adversely affected the drug's subsequent rate of uptake. The suggestion that this safety issue affected confidence in the other statins was supported by a plateau in the other statin curves for a short period around the same time. This period also coincided with safety issues that were arising with drugs in other classes.

- Generic challenge – Introduction of the category M tariff of the new Pharmacy Contract in April 2005, resulted in a significant reduction in the price reduction of generic simvastatin (genericisation of the market two years earlier had had little impact as prices had remained high). This coincided with an unprecedented NHS drive for restrictive prescribing policies and incentive schemes aimed at encouraging switching to generic simvastatin. The impact was observed as a virtually immediate plateau in the diffusion curves of atorvastatin and rosuvastatin.

- Subgroup targeting – From 2005 onwards, generic simvastatin 40mg took the majority of the atorvastatin 10-20mg market, (although it had less impact on the rosuvastatin 10mg market due to its greater potency that could not be achieved with generic simvastatin). The flattening rather than decline in the diffusion curves of the more potent statins however, demonstrated their retention of niche high risk patient groups.

Points of Divergence – Industry specified factors

- Clinician experience – The initial delay in the uptake of low dose statins was thought to be a consequence of clinicians needing a period of trial with them before realising their convenience in terms of ease of use. While the uptake rates for both atorvastatin and rosuvastatin were quite rapid, this factor may have caused a degree of depression that would not be easily discernible due to the scales represented by the curves.

- Health service environment – Respondents were conscious of the impending challenge from generic simvastatin, but they described how the unprecedented scale of the NHS drive for restricted prescribing policies advocating the use of generic simvastatin was unforeseen, which respondents explained left them unprepared for its impact.

- Impact of company mergers – The rapid uptake of atorvastatin was considered by respondents as reflecting the impact of a large field force of representatives that was required due to issues of scale for a drug that was predominantly prescribed in primary care.

- Response to safety concerns – The handling of the safety warnings for rosuvastatin by deflecting concerns was viewed by respondents as having potentially limited the drug's recovery. They believed a strategy using clinical evidence to align rosuvastatin with the rest of the class in terms of safety using the evidence to support their claims, would have been more effective in terms of converting clinical opinion. Wider pharmaceutical safety issues external to the class (e.g. withdrawal of COX II inhibitors in 2004) were considered to be a contributing factor in heightening an already cautious regulatory environment.

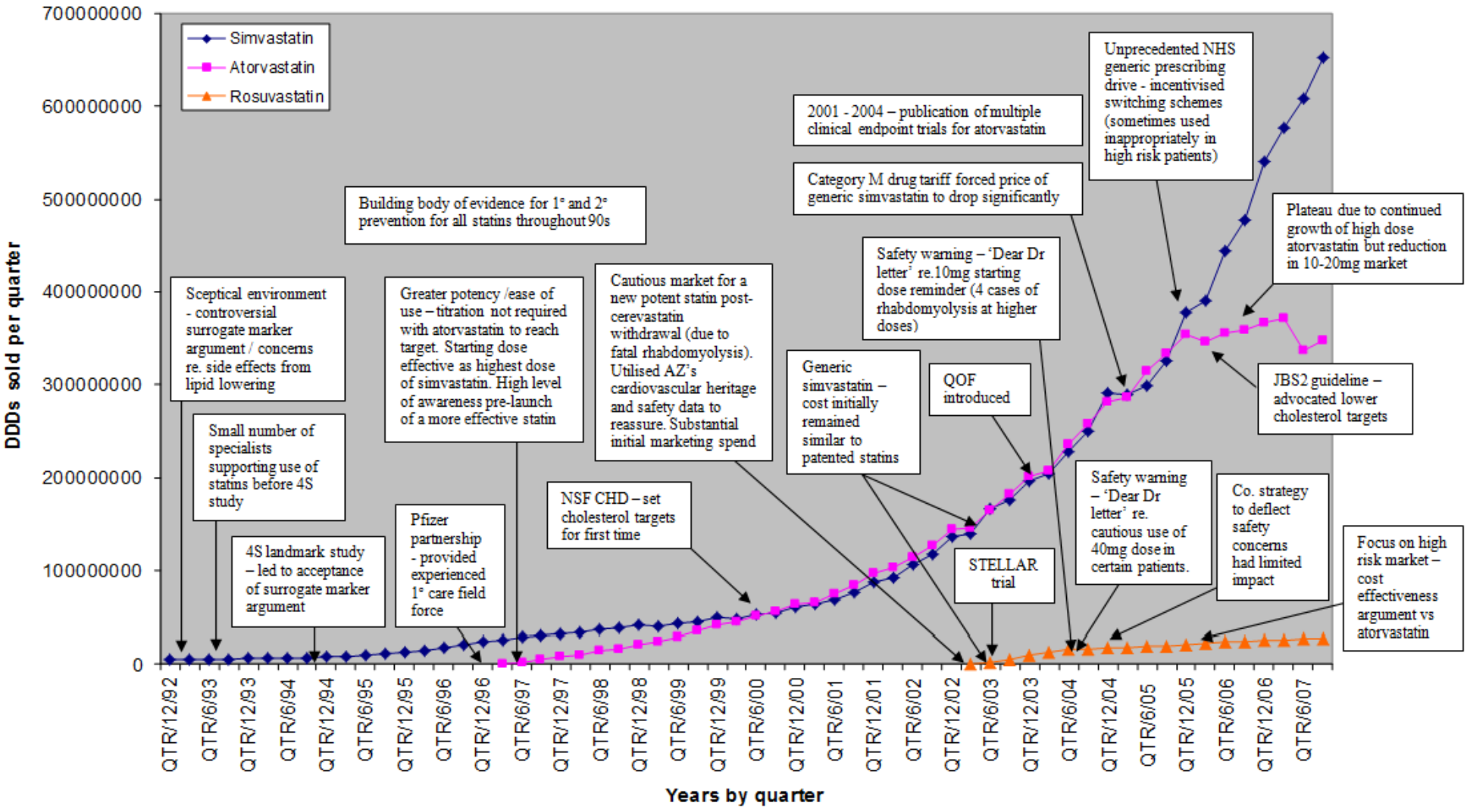
- Guidelines – Despite an extensive array of guidelines, respondents considered that their effect appeared to be cumulative in that they informed policy outcomes such as the NSF for CHD in 2000. Only the Joint British Societies guideline (JBS2) produced in December 2005 was mentioned specifically as having thought to have had a tangible impact on diffusion. It was the first in the UK to lower targets below that advocated by Government policy, which favoured the use of the more

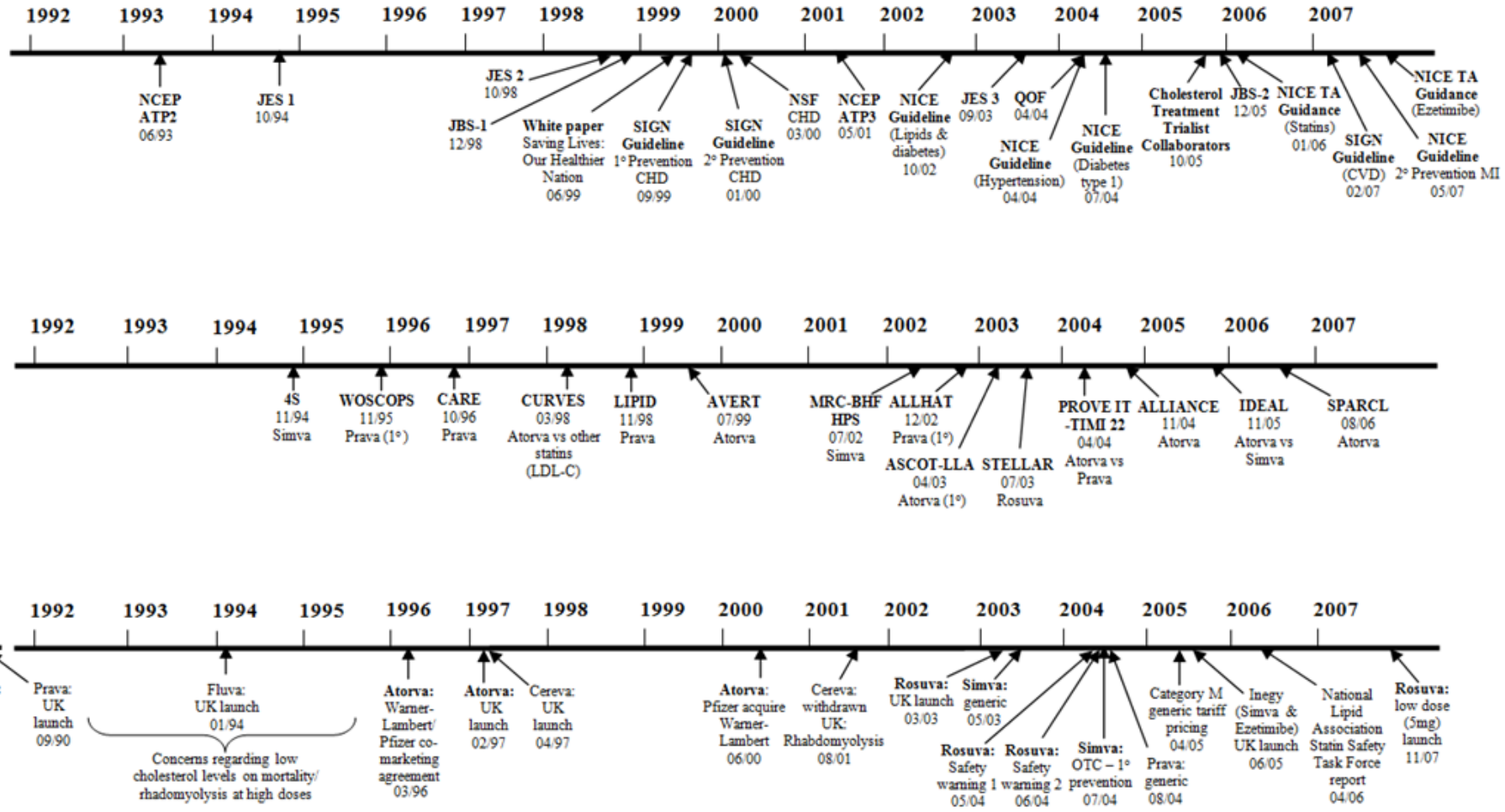
potent branded statins (policy maintained its original position despite respondents indicating they believed clinical opinion was moving towards lower targets).

6.4. Chapter comment

Diffusion curves, representing usage (as in this research) or sales, have limitations in informing studies on technology diffusion. They require augmentation with additional sources of information to obtain a comprehensive picture of the reasons why a drug did or did not diffuse. The NHS is a dynamic environment, with events involving multiple stakeholder groups occurring simultaneously that may have some bearing on the diffusion of a new drug. Even with the sophistication of time series analysis, it would only be possible to attribute pin point discrete events. The effects of multiple simultaneous events or cumulative effects that arise from socially driven factors (based on experiences or perceptions) would not be discernible, particularly as the data is only accessible by quarter after the fact. The accounts of Industry respondents have overall closely aligned with the literature and clinical expert accounts for all case studies. Where there have been points of divergence, this has contributed to enriching the understanding of the cases.

Figure 6.4: Statins - Composite Triangulation





CHAPTER 7

DISCUSSION AND CONCLUSION.

7.1. Introduction

This chapter i) outlines the novel contributions of the research, ii) summarises the key findings of the empirical research within the context of previous explicit Industry contributions to the academic literature iii) considers the implications of the findings and iv) discusses the potential for future research.

7.2. Novel contributions

7.2.1. Respondents

This is the first empirical study to gather, analyse and present views on diffusion influences from personnel currently working within pharmaceutical companies. In doing so, it has contributed an absent voice from the biomedical literature on this issue, which can co-exist as an alternative stakeholder perspective amongst the views and opinions of prescribers whose perspective currently dominate the discussion on pharmaceutical diffusion. One of the reasons why Industry perspectives have been missing is that they are a difficult group to access. The commercial sensitivity surrounding the nature of the information the pharmaceutical industry possesses has potentially instilled a degree of reticence on behalf of both researchers to explore this issue and Industry personnel, who may be suspicious of the researcher's intent, to participate. Rogers made the point in his book that "data gathering from the change agencies diffusing the innovation and/or the R&D organisations that produce the

innovations was not part of the prototypical diffusion study. Officials in such systems may be at least equally to blame for certain diffusion problems as are the potential adopters (who are the usual objects of diffusion). But it is not easy for diffusion scholars to study these officials".

Despite such an inherent challenge, it has been possible to gain access and obtain first-hand accounts from personnel actively operating within the Industry. This offers a more reliable insight into their beliefs compared with anecdotal commentary and critical assessments of their behaviour. A set of otherwise tacit views has been elicited that can contribute a valuable insight into the drivers and barriers to diffusion of pharmaceuticals according to this unique group, and how these can be interpreted. In exploring these explanations with Industry participants, the research has also made explicit aspects of the Industry's own perception of what they do to actively influence diffusion.

7.2.2. Methods

The use of quantitative data (diffusion curves) to test the validity of qualitatively derived Industry claims about pharmaceutical diffusion influences has not been done before. This is most likely a consequence of the need for significant upfront investment to generate sufficiently large numbers of diffusion curves, coupled with a lengthy access process to ensure that four case studies were eventually possible. Taking a case study approach imposed additional levels of complexity considering the main aim of the research was to obtain general themes that the Industry felt were influential in the diffusion of pharmaceuticals. However, there was a risk that in taking a general approach i.e. talking about diffusion influences in the abstract would

not have yielded the same depth of response achieved through drawing upon the wealth of examples offered by case studies. This was demonstrated by the fact that most of the empirical studies identified in the literature review posed questions about general concepts and typically achieved official line responses, which suggested the need for a new approach. Importantly, a general approach would not have offered the opportunity to triangulate the respondents' accounts with other data sources describing the same phenomena, which has enabled a richer picture to be generated.

7.3. Key findings

7.3.1. Industry themes affecting diffusion

The Industry perspectives demonstrated how they perceive diffusion to be influenced by a combination of both tangible and intangible factors. Ten general themes encompassing these factors were elicited across the four case studies and are discussed below. Additionally, the specific Industry perceived drivers and barriers of diffusion for each of the four case studies are summarised in Table 7.1.

Clinical need

For an innovation to diffuse, Industry respondents felt there had to be a genuine need and that no amount of marketing could make prescribers use something that was not needed. They distinguished clinician-interpreted need including discontent with current therapies or poor innovation to date and patient need. These may not be in alignment. In the PDE5 inhibitor case, the Industry's insight indicated that clinicians were more focussed on restoring function, whereas patients' priority was intimacy and normality. The daily preparations of the bisphosphonates were also highlighted as an area where patients' discontent was not fully recognised.

Clinician/patient experience

Clinician and patient experience with a drug was sometimes a strong feature of the Industry's response (absent from the Industry literature review, although not from Rogers' diffusion of innovations theory). Respondents highlighted several examples where changes to formulation were a significant driver of diffusion as they clearly improved the patient experience. Negative experience of the new drug was perceived as a major barrier to diffusion. The oesophageal irritation associated with the bisphosphonates (due to non-compliance with the complex dosing regimes, which is why this aspect had not been observed under the strict conditions of clinical trial settings) was perceived as a real limitation.

Clinical evidence

Evidence was cited as needing to fulfil various functions, from regulatory approval to marketing and had to offer novel, concise information that could be easily interpreted by specialists and generalists alike. Practical considerations, such as the return on investment on a limited patent life, may also dictate the nature of evidence provided and mean that studies that would be intuitively useful, for example head to head comparative trials, do not get funded. In these circumstances, surrogate endpoints were considered as relevant comparators. Evidence was also seen as having a temporal aspect. Publication of the Fracture Intervention Trials for example for daily alendronate made little impact on its diffusion curve at the time, but changes that occurred later in the lifecycle brought its relevance to the fore. The prestigious nature of the journal in which a study is published was also a matter for trade-off. Respondents discussed how the undoubted kudos from a high impact publication is

set against the more rapid dissemination and, perhaps, simpler messaging from a study in a journal that can publish more quickly.

Health service/policy environments

The inherent tensions that exist between the pharmaceutical industry and government, in that government both regulates the Industry and through the NHS acts as its main market, was a feature highlighted by respondents that acts to both enhance and retard diffusion. Respondents described how companies seek out links to policy and national initiatives, even when they may be tenuous (e.g. bisphosphonates and falls in the NSF for Older People). The effect of guidelines was also described as having varying degrees of influence on diffusion, often being more positive if they coincided with general trends in clinical practice. Conflicts were identified, for example in the statins case where the Joint British Society guidelines seemed to support use of the most potent agents yet government policy was pushing towards generic simvastatin. Clinical setting also exhibited tensions for respondents. The Industry will almost always want to move prescribing from specialists to generalists to accelerate diffusion due to the greater number of prescribers in primary care, but respondents described how this shift can be compromised by policy barriers as in the case of sildenafil, or reluctance on behalf of non-specialists to want to manage certain conditions they perceive to be outside their expertise (schizophrenia and osteoporosis). However, as it is the specialist who is most likely to be interested in new technologies, respondents recognised that driving treatments to a primary care setting may therefore reduce the number of treatments available to patients.

Adopter attitude

The view from respondents suggested they regarded UK clinicians as conservative in their practice, which can make them late adopters of new technologies, and encourages a sceptical view of information provided by Industry. Some respondents did acknowledge however, that challenging market access conditions could be a contributing factor rather than necessarily an ingrained culture. Attitudes that distinguish life-saving from life-enhancing treatments were perceived by respondents as having an impact on diffusion, as did clinician and patient perceptions of diseases. Diffusion of treatments for osteoporosis and erectile dysfunction was enhanced for example when clinicians were persuaded that the conditions were not an unavoidable part of ageing, or that the cause was physiological, and not psychological.

Communicating relative advantage

Respondents indicated that communicating relative advantage was a critical part of their remit, and the use of representatives was essential in this. Allowing two way exchange of information was supportive of the views on interpersonal relationships presented in the Industry literature and Rogers' diffusion of innovations theory. Respondents referred to Rogers' adopter categories to explain how they tailor their information materials, but did point out that the nature of information may change during the lifecycle of a drug. In the BP case advertising materials initially had a greater scientific focus to appeal to innovators, but then took a more compassionate approach towards the latter stages of the lifecycle to invoke the attention of the late majority. Failure to communicate relative advantage from the outset was seen as a major barrier to diffusion, as it is not possible to re-brand pharmaceuticals in the way

other products can be. A host of factors are implicated here including complex or changing messages, difficult dosage regimens and market entry position.

Market development

Market development embodies actions that respondents highlighted the Industry is involved in to delay the diffusion curve reaching its plateau. This involves both identifying the market needs during drug development and removing barriers to diffusion post-launch. Examples included diagnostic service provision (Fracture Liaison Clinics in osteoporosis), and company sponsored physical health training programmes for NHS staff managing patients with schizophrenia justified on the basis that weight gain was legitimately associated with the condition. In this case this helped to focus what was initially a drug-specific issue to a disease-specific issue. Dissemination of information via patient groups, public figures and the media, is also a commonly used tactic of market development, which was regarded by respondents as principally the responsibility of the market leader.

Key opinion leaders (KOLs)

KOL influence was notably absent from the Industry literature and yet this factor featured highly in the interview material. Their influence ran from early stage development through to ensuring collegiate support post-launch. Respondents stressed the need for KOLs to ideally be seen as at arm's-length from Industry, consistent with Rogers' detailed discussion on opinion leader influence. It is seen as critical to have the right KOL, in the right setting at the right stage of diffusion. In the case of erectile dysfunction, a negative diffusion curve inflexion was attributed to the company not fully appreciating that the main influencers were still those in the

specialist sector despite most prescribing decisions taking place in primary care. Interestingly, as in the case of osteoporosis, KOLs can originate from within the companies themselves, if the scientists who developed a class of drugs can be portrayed as the experts in that disease area. Competitors here saw that as compromising their own entry into a market 'owned' by another company.

Company cultural heritage/perception

Some of the cases highlighted the importance of how a company's approach to a market needs to be sensitive to the norms operating within that area. Respondents described how their cultural mindset is formed as a result of a heritage in certain disease areas. Launching into different disease areas with different social norms and structures but using long-standing strategies was considered by respondents to be a cause for some of the negative inflexions in the diffusion curve. Being seen as either very aggressive or very conservative by adopters in their approach to marketing was also perceived as a potential drawback. A cardiovascular approach to the osteoporosis market for example was not well received by adopters as it was thought by respondents to have been perceived as being too aggressive. Equally a conservative approach in the erectile dysfunction market was believed to have resulted in a limited impact. The key message therefore was a company's approach ideally needs to be responsive to the specific needs of the disease area into which the drug is diffusing.

Pricing

Pricing for first entrants was seen as relying on a skilful assessment of what a particular market will bear. For late entrants there is effectively a cap on prices

dictated by the others in its class, plus the threat of impending generic pressure, and yet the costs of R&D still need to be recouped. Price perception was highlighted as a potential barrier to the adoption of new drugs. Respondents believed that in circumstances where generics are involved as either the comparator (generic conventional antipsychotics vs branded atypical antipsychotics), or as a pre-existing formulation (generic risperidone vs Risperdal Consta), the branded drug will always be perceived as being expensive irrespective of any relative advantage it may afford. Perception can also be impacted on by the clinical setting. Respondents believed drugs limited to use in secondary care as a result of their administration (such as injectable risperidone) were under greater price scrutiny than those from the same class prescribed in primary care (e.g. oral olanzapine) despite being of equivalent or similar price.

Table 7.1: Summary of Industry Perceived Case Study Diffusion Influences

	Industry perceived drivers of diffusion	Industry perceived barriers to diffusion
Bisphosphonates	• New once weekly formulation alleviated the significant side effect issue • Ease of administration - impact of complicated regimen lessened by weekly formulation • Clinical need - lack of existing treatment options • Under-treated population	• Safety warnings - oesophageal irritation • Apathy towards disease recognition – not being considered a real/credible disease • Opinion leadership loyalty to one company • Co. approach to the osteoporosis market not commensurate with system norms • Overly-complicated trial design (stemmed from lack of experience in pharmaceutical field) • Under-diagnosed population
Atypical Antipsychotics	• Ease of use: simplicity of olanzapine's dosing regimen (single 10mg daily dose vs risperidone's need for titration) enabled it to benefit from unprecedented need • Unprecedented clinical need driven by innovation inertia • Side effects of AAs significantly less than current therapies • Safety alert resulting in withdrawal of a drug, for which AAs were substituted (off-label indication)	• Complicated trial messages leading to confusion about starting dose – intended efficacy not witnessed by clinicians • Safety warnings - off-label use in inappropriate populations • Price perceptions associated with secondary care drug administration • Negative associations with administering injection-based formulations • Emergence of new side effects • Perception of need for specialist management by non-specialists • Price competition with genetic conventional antipsychotics
PDE5 Inhibitors	• New more acceptable mode of administration – encouraged men to seek treatment • New formulation enabled non-specialist administration • Patient-driven need • Under-treated population • Unprecedented media attention and public interest in sexual topics • Recognition and acceptance that majority of ED cases have an organic and not a psychological cause – overcame stigma	• Restrictive government policy for NHS availability • Stigma associated with ED prevented patients coming forward for treatment • Policy limited prescribing to specialists – fewer prescribers compared with intended non-specialists • Media frenzy detracted attention from the seriousness of the condition. • Lack of clarity in terms of within class differentiation • Attitudes of apathy - ED considered as a lifestyle condition, or embarrassment from health professionals and patients to discuss condition • Misalignment between patient and clinician needs from a treatment perspective
Statins	• Growing acceptance that the lower the cholesterol level the better - emergence of an effective cholesterol lowering drug in statins • Enormous investment in clinical studies leading to transformation in prescribers' viewpoint - improved outcome in all cause mortality demonstrated by 4S trial • Trial suite included supportive independent study (Heart Protection Study) • QOF has driven statin use with financial incentives • Government policy (NSF/NICE TA) boosting further usage	• Safety warnings re: rhabdomyolysis (cerevastatin and rosuvastatin, but had class effect) • Very underdeveloped market shrouded in controversy during early 1990s • Emergence of a new phase (genericisation of older molecules - required implementation of Schedule M generic pricing restrictions before generic impact was observed) – compromised diffusion potential of later entrants • NHS Switching policies with financial incentives • Conservatism of government guideline targets • NHS drive for generic use unprecedented – function of the size of the market and chronic nature (vs other disease areas) making it a financial priority. Class with the most spend. • Fewer points of differentiation - higher doses in higher risk patients (reduced patient population)

7.3.2. Divergence and convergence between Industry views and case study literature and expert views (results of triangulation)

Clearly what Industry respondents said often overlapped with accounts about the case studies documented in the literature and supported by clinical experts. This suggests that respondents did not hold radically different perspectives on pharmaceutical diffusion from those elicited through other sources. But sometimes their views did diverge, which has provided some new insights into possible diffusion influences. The convergent findings were largely related to the more tangible factors that influence diffusion, such as pricing, changes to formulation that improve ease of use, safety warnings, government policies, clinical evidence, where it is easier to correlate the impact of an event with a time point on the diffusion curve (within the limitations of data interpretation, explained in previous sections). The divergent findings largely represented a combination of factors based on their insider knowledge (for example, impact of mergers on sales force dynamics; issues with journal restrictions; culturally influenced approach to market entry), and the more intangible factors they uncover from their efforts to understand adopter attitudes towards their products. Most of the barriers to diffusion that respondents highlighted had a social basis such as the detrimental impact of not fully appreciating the social dynamics of KOL influence in different disease areas; issues with communication that lead to unintended consequences; distorted adopter perceptions; and incompatibilities between patients' and clinicians' priorities. While these divergent findings are merely hypothetical in that they represent the world according to respondents, some of the more discrete events can be supported by the prescribing data represented by the diffusion curves.

7.4. Comparison of the Industry themes with prior Industry contributions to the literature

The literature review presented in Chapter 2 demonstrated that the only indication of pharmaceutical industry views on diffusion was from a relatively poor literature that only told part of the story (usually presented as counter-arguments to criticisms, rather than providing any depth of insight into their perspectives on wider diffusion issues), or inferences from critical commentaries on Industry practices. This was in spite of a wide search of the biomedical, marketing and economic literatures using a deliberately broad search strategy to try and capture their views. Relevant factors were drawn out by the literature review and presented under broad themes, but the only way to find out Industry perspectives was to research them directly.

Comparison of the ten general Industry themes derived from respondents with those from the Industry literature (Table 7.2.) demonstrated that the degree of overlap was such that all of the literature review themes could be incorporated within those discussed by respondents. The literature review presented a limited picture of what respondents obviously had a much greater depth of knowledge and insight of. In these instances, the research has been able to support and augment topics that were not previously covered in depth, providing insights into how companies proactively respond to diffusion barriers and actively influence others.

There were however, new themes not documented before in the Industry literature, which included the more tacit, socially driven aspects of diffusion, such as the influence of clinician and patient experiences with new drugs, the attitudes of clinicians and patients towards diseases and the social norms that exist with regards to disease management, the impact that can have if company approaches to markets are not fully

commensurate with disease-specific norms, which requires an understanding of KOL influence i.e. needing to introduce the drug in the right way, to the right people that have the right influence.

Table 7.2: Literature and empirically-derived Industry themes on key diffusion influences

Empirically derived themes (order as presented in Chapter 5)	Literature review themes
Clinical need	Research and development
Clinician/patient experience	-
Clinical evidence	Medical research
	Safety and regulation
Health service/policy environments	Government priority
Adopter attitude: clinician/patient	-
Communicating relative advantage	Marketing and promotion
	Competitors/generics
Market development	Diagnosis
	Patient influence
	Mass media
	Supply
Key opinion leaders	-
Company cultural heritage/perception	-
Pricing	Cost impact/ HTA

While some of these new themes are not essentially 'new' in that they have been acknowledged as being influential in the wider diffusion literature, they are novel contributions in that they are offering pharmaceutical industry perspectives on these factors that have not been elicited in the Industry literature before.

7.5. Insights and contradictions

Some of the more unexpected insights of the research included the suggestion that the practices of non-specialists created access barriers to pharmaceuticals through inappropriate referrals to secondary care; the potential incompatibilities between clinician and patient perspectives; the assertion that embarrassment is a major barrier for clinicians and patients fully discussing treatment options for sensitive conditions

(unlikely to be admitted by clinicians themselves in diffusion studies); that new formulations may be rejected on the basis of irrational negative associations; and that flawed communications were believed to have distorted clinician perceptions, such that new drugs were positioned inappropriately, or gave rise to safety issues. Safety issues were particularly interesting as in most examples they were conceptualised by respondents as not being a consequence of the drug itself, but more about the way the drug was being used, which is a perspective that absolves a degree of responsibility. There was an acceptance however, by respondents that communication issues around a lack of clarity in the messages they were conveying was a major part of the problem that led to inappropriate use.

Certain perspectives that were presented could be viewed quite cynically such as changing the way diseases are perceived and the development of services to support diagnosis, in that the ultimate beneficiaries are the manufacturers of the drugs that are prescribed to manage the condition. However, if the drugs are demonstrated to be efficacious, there is a benefit to the patient and the health service from these Industry funded services as patients are being diagnosed that otherwise would not be. I also do not think it was necessarily detrimental to change attitudes towards marginalised conditions such as osteoporosis and erectile dysfunction, as the shift in the perception of clinicians and patients has resulted in many people benefitting from access to treatments for these conditions.

I think some of the issues raised by respondents offer plausible explanations about pharmaceutical diffusion. However, when viewed critically there are tensions within some of the arguments presented. These are outlined below:

7.5.1. Plausible arguments:

Comparative trial design – The assumption that comparative trials are not conducted by Industry for fear of demonstrating inferiority was not confirmed by Industry respondents. They instead presented an alternative perspective around the commercial pressures they have to take into consideration. For instance, it is not always financially viable for them to conduct comparative trials if they are unlikely to report sufficiently ahead of patent expiry for them to benefit from the substantial investment. If this is indeed the barrier to conducting comparative trials, that are so very much needed by clinicians, then we are left with a scenario of either requiring more publicly funded trials to plug the gaps in research, or conditions have to change that make it more conducive for companies to want to do this type of trial design. Perhaps models could be considered where patent exclusivity is extended to give companies time to conduct head to head studies and recoup some of the costs involved. However, this would involve a trade-off between generating the evidence people want to make informed prescribing decisions, and delaying the emergence of a generic market. The risk of demonstrating inferiority is likely to be a concern, but equally there is a significant reward for superiority. If there is a genuine belief that the product is good enough and meets genuine need, as is often claimed, there is an incentive for these products to be assessed in this way. This may also reduce the incentive to produce me-too drugs if the relative advantage is not sufficiently substantial. If left to the Industry to conduct these trials, however issues will remain such as choice of appropriate comparators in a global market.

Clinical need – While there is a lot of scepticism around whether new pharmaceuticals are produced in response to a genuine clinical need, the fact that respondents believed

clinical need is an adopter-defined, and not a manufacturer-defined concept is something I think is plausible based on this research. There were several examples cited where new formulations of existing drugs developed in the belief they were answering a clinical need did not diffuse successfully because that need was perceived as either not there, or the drug did not align with the expectations of clinicians (exemplified by the intramuscular injection of long-acting risperidone). In addition, attempts described by respondents to change the meaning of clinical need for adopters (e.g. redefining efficacy in terms of long-term effects as opposed to immediate benefits) were unsuccessful as clinical need appears to be a factor that is conceptualised by the adopter.

Unique insights and active involvement – I think the insights that respondents provided in relation to strategies that did not work as well as expected, such as communication issues and implications of misaligning company approaches to market entry with the social norms and systems of a disease area, do have some degree of plausibility on the very basis that there was nothing to be gained from their perspective by highlighting these issues and yet they provided some of the most fascinating insights. So did the discussions around the strategies companies use to accelerate adoption, such as subsidy of diagnostic or supportive services that coexist alongside the NHS, public policy engagement to engender favourable political and clinical environments and the impact of sales force dynamics on the diffusion curve. Company perception was a factor respondents were conscious of particularly as a result of attention levelled at the Industry in recent years pointing to unethical practices. Some critics of the pharmaceutical industry however, appear to miss a key point that would incentivise companies strongly against questionable activities. The most important statistic for these organisations is the share price. It is the one thing that CEOs are judged against,

indicates the confidence of the market in a particular company and ensures protection against hostile takeovers. Share prices are notoriously sensitive to reputational issues and scandals emanating from unethical behaviour, whether in research or commercial operations and almost always reflect negatively in the share price damaging the commercial viability of the company.

These insights from respondents clearly demonstrate the active role of the pharmaceutical industry in dissemination, but the unintended consequences of diffusion, exemplified by some of the highlighted safety concerns, indicate that social influences (such as sharing of clinical experiences that may have resulted in use of incorrect doses) were also at work.

7.5.2. Contradictions

The tension that exists within some of the Industry arguments however, does lead me to challenge some of their perspectives:

Experience –The insistence that clinical evidence is at the forefront of decisions about pharmaceutical diffusion did not align with the importance that respondents then placed on clinician and patient experience. The widely held view amongst respondents that clinicians need to observe the beneficial or harmful effects of a drug for themselves before they are convinced of its usefulness can be challenged by the fact that in many cases clinical outcome (e.g. prevention of fractures in osteoporosis or reduction of risk in cardiovascular disease) cannot be directly observed by the clinician. In the bisphosphonate case for example, it can take many years to see the effects of BPs on fracture reduction. Experience in this context is likely to reflect other experiential

factors such as improved patient tolerability, or improved ease of use rather than a need to observe efficacy. Clinical evidence therefore is likely to hold greater importance in decision making when the effect of drugs cannot be observed directly by serving as a vicarious trial for individual prescribers. However, there are different kinds of clinicians, some who prefer evidence and some who do not.

Key opinion leaders – Tensions exist between the suggestion that opinion leader loyalty hindered diffusion of competitor drugs in the bisphosphonate case study, when respondents then make the point that the only way KOLs retain their credibility is to maintain distance from any one company. It is difficult to find supporting or refuting evidence for this factor, but while criticisms remain that the Industry is 'creating' diseases, the scenario where expertise could originate from within a company is a potential competing explanation for competitor diffusion barriers.

Conservatism – The view that conservatism is a cultural characteristic of UK adopters can be somewhat challenged by different rates of adoption in different disease areas. It is therefore unlikely to be an ingrained cultural response, but influenced more by the particular environmental conditions that prevail in different disease areas. With regard to international comparisons of adoption rates, the structural barriers to market entry in the UK are a more plausible explanation for the differences, which some respondents did acknowledge.

7.6. Implications of the research

This research has elucidated an implicit perspective on diffusion that has only previously been touched on in the academic literature. It is important to attempt to

understand Industry perspectives as this is the only way we can gain an insight into why pharmaceutical companies behave in the way that they do. Making assumptions about their motivations, as opposed to empirically gathering their views, just because they present a challenging sector to research has led to polarised and inaccurate accounts prevailing. The pharmaceutical industry has not helped its position by only minimally engaging with the academic literature. This research therefore has provided an opportunity to engage and understand their perspective, presented within the context of additional sources of information describing the same phenomena, such that it can be viewed critically.

In addition to the academic contributions of this work, there are potentially some practical implications. There has been increasing emphasis in the UK on collaborative working between government funded agencies and the pharmaceutical industry to foster innovation and improve patient care (Department of Health/ABPI, 2010). While it is necessary to be mindful of the individual agendas each stakeholder group may bring to a discussion on diffusion there is value in exchanging and appreciating alternative perspectives. Some will remain sceptical as to the motivations of Industry as a partner in providing patient care as opposed to a supplier of it (Moynihan, 2012), but they certainly possess knowledge and resources that can be utilised by the health service. Through partnership, a dialogue can be established that recognises the needs of both sides, including understanding the realms of what is possible, what is not possible and the explanations for why certain things may not be possible, instead of assuming the stance that Industry is being uncooperative. While we have a good understanding of prescribers', payers' and Government's challenges, this research can contribute in some

way to understanding the issues in diffusion the Industry consider to be important and some of the challenges they face as the diffusers.

In addition to obtaining a greater understanding, this research has practical implication with regard to the methods used by the NIHR Horizon Scanning Centre (HSC). The NIHR HSC provides timely information to policy makers about significant new and emerging health technologies. It is the largest of the horizon scanning agencies and as such has a strong research focus, leading on the development of methods in horizon scanning that are disseminated amongst the other agencies. To ensure that we are carrying out the work effectively, we constantly strive to improve on the methods used. The NIHR HSC's current prioritisation criteria are based on previous diffusion work that has focussed on clinical, health service or policy-based opinion (Stevens *et al*., 1997; Booth-Clibborn *et al*., 2000; Cook *et al*., 2004; Packer *et al*., 2004; Packer *et al.*, 2006), the premise being that to predict with a degree of accuracy which new technologies are likely to have a significant impact on the NHS, it is first necessary to gain a comprehensive understanding of the factors that have influenced uptake and diffusion in the past. Eliciting Industry insights on diffusion influences has provided an additional source of information to further refine the NIHR HSC's prioritisation criteria for identifying new technologies.

7.7. Further research

The fact that a lot of the findings were confirmatory, coupled with the practical challenges this research presented, might dissuade me from recommending further research of this nature, particularly as access was most likely made possible through the established links that existed between the organisation I work for and the

pharmaceutical industry. However, I do think it was important to provide Industry respondents with an academic forum within which to discuss some of their challenges in relation to pharmaceutical diffusion, and make people aware of the environment in which they operate, which holds different pressures to the environment in which clinicians operate.

The significance of the less tangible factors in pharmaceutical diffusion indicates more studies of a qualitative nature are justified to uncover these potential barriers and drivers that cannot be exposed through quantitative means. Further qualitative exploration that could emanate from these findings includes:

i) Testing the Industry perspectives with clinicians to see if what they are saying rings true with them. As well as individual clinicians, the establishment of new stakeholder groups, such as the Clinical Commissioning Groups, whist heavily influenced by GPs, will be operating under a new dynamic. Additionally, the emerging architecture from *Innovation, Health and Wealth*, the white paper addressing improvements in the systematic introduction of innovations (Department of Health, 2011), will provide new stakeholders, such as the NICE Implementation Collaboratives and the Academic Health Science Networks (AHSNs) with alternative insights into diffusion against which the Industry perspective can be compared;

ii) Exploring how the marketers' insights on diffusion factors correlate with those of different employee groups within pharmaceutical companies, such as pharmacologists and Industry clinicians (providing further Industry access was possible);

iii) As part of a much wider application, the findings could be compared against the various other models that exist on diffusion research to contribute to extending theories on diffusion.

7.8. CONCLUSION

Pharmaceutical industry views on diffusion were regarded as a ‘black hole’, but in fact many of the respondents’ views were consistent with what was already known on diffusion. While this could be considered a product of obtaining official line responses, the fact that respondents were prepared to discuss their own role in diffusion and not only talk about the successes but some of their disappointments, offered a far greater insight than what was initially anticipated from this research. Unsurprisingly, their perspectives cast the Industry and their practices in a good light, which will inevitably be contested by other stakeholders. However, in amongst the rhetoric there have been some fascinating insider insights that are useful contributions to the diffusion debate, particularly with regard to the significance of the less tangible social interactions that can inform perceptions of new pharmaceuticals.

APPENDICES

Appendix 1: Literature Review Search Strategy

Literature review question:

What literature exist describing pharmaceutical industry views on important factors in the diffusion of drugs (direct accounts from Industry personnel or empirical studies involving Industry personnel)?

1. Databases searched:

The following databases were selected on the basis of their relevance to the research disciplines covered by the literature review topic.

	Database (Host)	Relevant disciplines	Date range
1	MEDLINE (Ovid)	Health and Biomedical Sciences, Social Science, Business and Law	1946 to Sep wk 1 2012
2	EmBASE: Excerpta Medica (Ovid)	Health and Biomedical Sciences	1974 to Sep 2012
3	Health Management Information Consortium (HMIC)[28] (Ovid)	Health and Biomedical Sciences	1979 to Jul 2012
4	Web of Science (ISI) Science citation index Social science citation index Conference Proceedings	Health and Biomedical Sciences, Social Science, Business and Law	 1899 – Sep 2012 1898 – Sep 2012 1990 – Sep 2012
5	EconLit (EBSCO)	Social Science, Business and Law	1964 to 2012
6	Business Source Premier (EBSCO)	Social Science, Business and Law	1907 - 2012
7	ABI/INFORM Global (Proquest)	Social Science, Business and Law	1933 - 2012
7	Applied Social Sciences Index and Abstracts (ASSIA) (Proquest)	Social Science, Business and Law	1987-2012
8	Dissertations and Theses (Proquest)	All	1861 to present day

[28] Compilation of data from the Department of Health Library and Information Services and King's Fund Information and Library Services.

2. Search strategy:

According to the Cochrane Reviewers' Handbook, when developing a search strategy:

- It is always necessary to strike a balance between comprehensiveness and precision. Increasing the comprehensiveness of a search entails reducing its precision and retrieving more non-relevant articles.

- Developing a search strategy is an iterative process in which the terms that are used are modified, based on what has already been achieved.

- There are diminishing returns for search efforts; after a certain stage each additional unit of time invested in searching returns fewer references that are relevant to the review. Consequently there comes a point where the rewards of further searching may not be worth the effort required to identify the additional references.

Rationale

Several authors who have assessed the evidence in the field of diffusion of innovation research have indicated that formal protocol-driven search strategies may fail to identify important evidence (Greenhalgh *et al*., 2005; Greenhalgh and Peacock, 2005; Robert *et al*., 2010). The nature of this literature review topic required a combination of broad MeSH headings combined using Boolean operators with specific title searches in order to obtain the most relevant yield.

The search strategy was tested for several variables to assess the impact on the yield. These included focussing and exploding MeSH headings and broadening title searches to include abstracts or text words. The 'diffusion of innovation' MeSH heading, or the use of truncated diffusion synonyms (diffuse* OR adopt* OR uptake OR sales OR market* OR disseminat* OR commerciali* OR penetrate*) when applied to the dataset limited the yield of relevant articles significantly. The iterative development of the search strategy is presented in section A. The final search strategy that obtained the most relevant yield and was subsequently applied across other databases is presented in section B.

A. Iterative development of the Literature review search strategy

Relevant MEDLINE MeSH Headings:

MeSH	Scope	Used for
DRUG INDUSTRY	That segment of commercial enterprise devoted to the design, development, and manufacture of chemical products for use in the diagnosis and treatment of disease, disability, or other dysfunction, or to improve function.	pharmaceutic industry pharmaceutical industries industry pharmaceutic industry pharmaceutical pharmaceutic industries drug industry industries pharmaceutical industry drug industries drug

		drug industries industries pharmaceutic pharmaceutical industry
DIFFUSION OF INNOVATION	The broad dissemination of new ideas, procedures, techniques, materials, and devices and the degree to which these are accepted and used.	innovation diffusion diffusion of innovation diffusion innovation

Database: Ovid MEDLINE(R) <1946 to September Week 1 2012>

#	Searches	Results
1	*Drug Industry/	16137
2	(Perspective* or View* or Overview* or Insight* or Perception* or Mindset* or Attitude* or Impression* or Thought* or Belief* or Realit* or Observation* or Angle*).ti.	365129
3	1 and 2	694
4	limit 3 to English language	615
5	from 4 keep 1,7-8,13,15-16,18,29-30,33,39,56,60,65,67,76,86,91-92,105,125,134,137,147,156,166,171,180,203,205,219-220,223,226,228,232,240-241,245,253,261,266,274-276,281,290,302,304,306,314,321-322,327,329,336,338,345-346,350,352-354,357,364,367,392,395-396,399,408,411,421-422,432,436,443,462,469,475,478,480,490,493-494,501,506-507,512-513,518,521,526,528,542-543,549,551-552,559,566,570,579-581,583-584,586-590,593,599-600	115
Testing the Search strategy		
Apply consecutive terms filter to reduce hand searching requirement		
6	([pharma* industr*] or [pharma* compan*] or [pharma* manufactur*] or [pharma* sponsor*] or [drug* industr*] or [drug* compan*] or [drug* manufactur*] or [drug* sponsor*]).ti.	3389
7	4 and 6	149[29]
Assess impact of broadening title terms to include also abstract terms		
8	(Perspective* or View* or Overview* or Insight* or Perception* or Mindset* or Attitude* or Impression* or Thought* or Belief* or Realit* or Observation* or Angle*).ti,ab.	1842381
9	1 and 8	1528
10	9 not 5	1413[30]
Apply 'Diffusion of innovation' MeSH heading and Diffusion Synonyms filters		
11	Diffusion of Innovation/	12567
12	4 and 11	4[31]
13	1 and 11	92[32]

[29] There was a degree of overlap with search 5, but many articles included views on the pharmaceutical industry from other stakeholder perspectives (clinicians/medical students/patients) and not Industry themselves. Several key studies were missing from search 5, therefore it was not a suitable filter.

[30] No more additional useful articles identified. No need to go any broader than perspective synonyms in title.

[31] Focus was too narrow.

14	(adopt* or uptake or diffus* or launch* or market* or disseminat* or commerciali* or penetrat*).ti,ab.	808842
15	11 or 14	808842
16	4 and 15 *(Drug industry MeSH + 'perspective 'synonyms ti.+ 'diffusion' synonyms ti,ab.)*	132[33]
17	9 and 15 *(Drug industry MeSH + 'perspective 'synonyms ti,ab. + 'diffusion' synonyms ti,ab.)*	453[34]
18	5 and 16	25[35]
19	16 not 5	101[36]
Identifying empirical studies		
20	(questionnaire* or survey* or interview* or qualitative).ti,ab.	843202
21	4 and 20	97[37]
22	5 and 21	13[38]
Broadening the empirical study search		
23	1 and 14 and 20 *(Drug Industry MeSH + diffusion' synonyms ti,ab. + interview synonyms ti,ab.)*	196
24	limit 23 to english language	174[39]

B. Final search strategy applied to other databases

The MEDLINE search strategy (presented below) was adjusted as necessary (including equivalent MeSH terms) for the other electronic database searches.

#	Searches	Results
1	*Drug Industry/	16137
2	(Perspective* or View* or Overview* or Insight* or Perception* or Mindset* or Attitude* or Impression* or Thought* or Belief* or Realit* or Observation* or Angle*).ti.	365129
3	1 and 2	694
4	limit 3 to english language	615
5	from 4 keep 1,7-8,13,15-16,18,29-30,33,39,56,60,65,67,76,86,91-92,105,125,134,137,147,156,166,171,180,203,205,219-220,223,226,228,232,240-241,245,253,261,266,274-276,281,290,302,304,306,314,321-322,327,329,336,338,345-346,350,352-354,357,364,367,392,395-396,399,408,411,421-	115

[32] Majority of the yield was not relevant.
[33] Limited number of Industry perspectives – mainly clinical views on Industry
[34] Broadening to include 'perspective' synonyms in 'title' and 'abstract' did not yield any further useful references.
[35] 25 records were common to both sets.
[36] Additional yield containing diffusion references were not relevant.
[37] Empirical studies, but focus was too broad.
[38] Of the hand-selected studies, 13 were empirical studies involving the pharmaceutical industry.
[39] Broadening the empirical study search did not increase the relevance of the yield.

	422,432,436,443,462,469,475,478,480,490,493-494,501,506-507,512-513,518,521,526,528,542-543,549,551-552,559,566,570,579-581,583-584,586-590,593,599-600	
6	(questionnaire* or survey* or interview* or qualitative).ti,ab.	843202
7	5 and 6	13

3. **Intuitive searches**: Formal search strategies were accompanied by more intuitive approaches including:

    a. **Pearl Growing:** This search technique uses one relevant article as the basis for finding other relevant articles (either through the 'find similar' or electronic citation indexing functions), which identified a small number of additional articles.

    b. **Serendipitous discovery:** Browsing and being alert to serendipitous references (as advocated by Greenhalgh *et al*., 2005).

4. Specific Journal Searches

As an additional method, a limited number of journals that featured key publications were also searched using keyword search terms.

- BMJ
- NEJM
- JAMA
- Lancet
- Journal of Medical Marketing: Device, Diagnostic and Pharmaceutical Marketing
- Health Marketing Quarterly

5. Grey literature

a. **OpenGrey (formerly SIGLE)**
While some of the databases listed above (e.g. ABI/Inform, ASSIA) incorporated both peer-reviewed scholarly journals and grey literature, a search of the grey literature database OpenGrey (http://www.opengrey.eu/) was conducted with the broad headings of the main search strategy, but yielded few results.

b. **Trade publications**: Monthly trade magazines (PharmaTimes Magazine and Scrip Magazine) and online trade news sources (Pharmaceutical Marketing Live (PMLive)) - identified predominantly normative style articles.

6. Internet searches

Keyword and consecutive term searches (consistent with those tested in MEDLINE) were conducted in Google and Google Scholar. Search strings were refined iteratively in response to emerging data.

Search Results:

A total of 153 articles that provided data on the subject question were retrieved, 90 of which were included in the review. While the search strategy was purposefully kept broad to capture relevant articles, there was no way of identifying Industry–authored papers that did not specifically state that it was an Industry response in the title or abstract. Searching for individual company names was considered too specific a limitation to incorporate into the search strategy.

Twenty five empirical studies were identified that aimed to elucidate Industry views, usually on just one factor in the diffusion process. The remainder consisted of Industry opinion pieces, predominantly from the major pharmaceutical companies Merck, Lilly, GSK and Pfizer, reflecting similar niche focuses in the diffusion debate (most commonly from a USA perspective), or Industry evidence submissions to the HCHC Inquiry. Areas commonly discussed were in relation to research and development (R&D), regulation, pricing and HTA, clinical trial design and the perceived educational role of the pharmaceutical industry. One article provided a discussion of a range of diffusion influences across the lifecycle of a drug, but this was a rare insight provided by an Industry employee on a single drug.

Appendix 2: Industry Feasibility Study Response

Pharmaceutical companies approached to determine the feasibility of Industry participation in the research.

Company	UK Market Position (in 2002)	Response
GlaxoSmithKline	1	Needed further clarification in order to know what they could supply, but willing to participate.
Pfizer	2	Positive commitment to participate if possible.
AstraZeneca	3	Positive commitment to participate if possible.
Merck Sharp & Dohme	4	Needed further clarification in order to know what they could supply, but willing to participate.
Novartis	6	Positive commitment to participate if possible.
Aventis	7	Positive commitment to participate if possible.
Abbott	16	Needed further clarification in order to know what they could supply, but willing to participate.
Lundbeck	20	Unable to agree to participate at this stage as individual brand managers would need to be contacted for case study drugs once known.

Appendix 3: Approach email to case study experts - selection criteria

Dear [Expert]

My name is Luan Linden and I work with Dr Claire Packer at the National Horizon Scanning Centre. Claire has suggested that I contact you in the hope that I may be able to ask for your assistance.

I have recently registered to do a Ph.D. investigating the views of the pharmaceutical industry on drug diffusion in the UK. The first step is to identify suitable case studies. Once identified, I will contact various data providers to construct a diffusion curve. I will then (a) explore the effect the pharmaceutical company had on diffusion through investigating marketing campaigns and talking to clinicians etc. and then (b) explain the shape of the curve through identifying key trials, guidelines, market competitors etc. In attempting to identify case studies, I have been overwhelmed by the vast number of possibilities. Although I have tried to apply selection criteria to narrow down the search, I am concerned that there is the potential to miss some interesting case studies and therefore I would like to tap into experts' for some guidance in making a selection.

If you are willing and able to assist me in this task, my only selection criteria are that the drugs should have been launched in the UK approximately between 1990 and 2000 and that they were intended for use in primary or secondary care (not over the counter preparations). Please do not feel that the selection has to only include 'blockbuster' drugs or those reviewed by NICE. The selection can include individual drugs or classes if you feel they would make a more interesting study. I have excluded proton pump inhibitors, COX II inhibitors and thrombolytics as other researchers have investigated these topics, but please consider any other specialties or patient groups of varying sizes.

The hard part is to define what I mean by 'interesting'. It encompasses a range of factors that could impact upon the diffusion of a new drug, including issues surrounding:

- Cost (or cost-impact) of the new drug compared with current treatments (more expensive/ much cheaper)
- Evidence base associated with the new drug (clinical reluctance due to limited faith in evidence/ rapid conversion in clinical practice as a result of several positive large scale trials)
- Side effect profile of the new drug (better/ worse)
- Administration (changes to mode or dose compared with existing treatments) causing increase/decrease in patient compliance
- Disease profile (is the new drug intended for life threatening/ non-life threatening indications)
- Need for patient monitoring with use of new drug (increase or decrease)
- Were there any later additional indications that expanded the new drug's market?
- Significant journal/media attention surrounding the introduction of the new drug (positive/ negative)
- Adverse drug reaction profile of the new drug (worse/ better) compared with existing treatments.
- Marketing campaign (do you remember any drug where its launch was associated with a particularly aggressive marketing campaign?)

- What type of company was behind the new drug's launch? (large/ small)
- Patient group interest in the new drug
- Did the introduction of the new drug result in service re-organisation issues (nurse prescribers as opposed to clinicians, home administration as opposed to medically assisted administration)?
- Geographical availability (uneven/even) of the new drug as a result of local/ regional decisions (price discounting etc.)
- Presence of official guidelines (NICE/NSF), independent assessments (UKMi), local/regional decisions (PCT committees)

Examples of drugs that address some of the above issues include Viagra due to the significant media and patient interest it received at launch; statins and Glivec due to the significant cost impact their introduction was going to have on the NHS; ondansetron and granisitron's uneven geographical availability due to cost and local discounting arrangements; and troglitazone due to its significant adverse effect profile.

I would be very grateful if you could suggest up to 10 drugs (including any of the examples used above if appropriate), bearing **some** of the above issues in mind, with a brief explanation (1-2 lines) as to the reason for your choices, ideally before [1 month deadline].

In addition to yourself, I am also asking experts from national and local prescribing committees (National Prescribing Centre, UKMi), representatives from the pharmaceutical industry, the ABPI, independent medical journalists, academia and public health and pharmaceutical advisors to assist me with this task, with the aim of trying to identify themes from the suggestions provided.

I appreciate that this is a very difficult exercise and I understand if you feel you simply do not have the time. Perhaps if you are unable to help on this occasion you can suggest a colleague who may be willing?

I look forward to hearing from you.

Kind regards

Appendix 4: Approach email to NIHR Horizon Scanning Centre Pharmaceutical Industry Contact

Dear [Industry contact name]

My name is Luan Linden and I work with Dr Claire Packer at the NIHR Horizon Scanning Centre at the University of Birmingham. I am writing to you in my capacity as a Ph.D. student to request your help in identifying a contact within your company who would be willing to spare the time to talk to me about marketing strategies employed by the pharmaceutical industry, with particular reference to [drug name/ or multiple drug names], which has been chosen as one of my case study drugs from an earlier prioritisation exercise.

In view of the detailed nature of the interviews, ideally I would need to speak to someone with knowledge of the brand history, therefore the marketing director may be my best place to start. So as to not provide unnecessary details to our horizon scanning contacts, I usually send a description of the research project to the marketing contact once identified, but in essence I am trying to obtain the pharmaceutical industry's perspective on what you think are the most important factors that impact upon the way a pharmaceutical is taken up into the market, using the case study as an example.

I would be very grateful if you could provide me with the relevant contact details at your earliest convenience, but if you have any questions please do not hesitate to give me a call.

Kind regards

Appendix 5: Approach email to potential pharmaceutical industry interviewee

Dear [potential interviewee name]

I am currently researching for a Ph.D. on the views of the pharmaceutical industry on the diffusion of drugs in the UK at the NIHR Horizon Scanning Centre, based at the University of Birmingham. We are a unit funded to provide the Department of Health with advance notice of new technologies that may impact upon the NHS in the next 2-3 years and part of our work feeds into the NICE programme. This 'early warning' is our main activity, but in addition we engage in an active research programme. One of our particular areas of interest is the adoption and diffusion of healthcare technologies.

I have been given your name as a contact by [name: industry contact/intermediary industry contact], [Business title] of [pharmaceutical company] as someone who may be willing to help with a brief, relatively informal one to one interview. Part of my research involves engaging directly with key industry personnel with the intention of gaining an objective insight into the process of drug uptake and subsequent diffusion from the perspective of the pharmaceutical industry. The key points of the research and the interview are summarised in the attached information sheet.

If you are able to participate, I am more than happy to travel to you at a time that is convenient, and I will follow-up this letter with a phone call in the next week to discuss any issues you may have prior to arranging an appointment ideally before [date – within approximately two months of request].

If you would like to discuss any aspect of the interview with me in the meantime, I have included my details below so please do not hesitate to get in touch. Otherwise I will endeavour to contact you in the next week.

Kind regards

Appendix 6: Company Information Sheet

(attached to email request in Appendix 5)

INFORMATION SHEET - Industry Interviews

What is the research about?

The aim of the Ph.D. is to elicit the views of the pharmaceutical industry on the factors that influences the uptake and subsequent diffusion of drugs in the UK. The pharmaceutical industry is the single most important data source in understanding diffusion and yet it is significantly under-researched. This is a topical area in the academic literature with many publications discussing influences on physicians' prescribing behaviour, but there is little documented from the industry's perspective. From a research point of view this would be of great interest, as it would represent the position of the people primarily involved in initiating and driving diffusion, as opposed to relying on second-hand accounts of the industry's role. By using a case study approach with actual diffusion curves as a vehicle for capturing the industry's viewpoint, the aim is to generate a comprehensive view of the factors that impact on a drug's diffusion.

What will be covered in the interview?

Various topic areas may be covered, including:

1. General issues such as:
   - what makes a successful marketing strategy and how marketing techniques used change throughout a drug's lifecycle;
   - the relative importance of different information sources (e.g. clinical trials/ systematic reviews) and methods of communication
   - the most important influencing factors at launch compared to the time periods that follow and;
   - how changes in the NHS have impacted upon industry practice and targets.

2. In addition, I would like to talk about a case study drug manufactured by your company. Some preliminary work has been done to construct a diffusion curve for [drug name] so it would be of interest to hear your experience/views of how the general issues can apply to an actual example.

What are the advantages of participating in this research?

If you agree to participate in this research, it will provide you with an opportunity to:

- Express views and opinions from a perspective that is not currently well represented in the academic literature.
- Further the understanding of individuals involved in healthcare with regards to the industry's role in research and development processes, launch, and post-marketing activities.
- Possibly help to redress the balance of criticism aimed at the pharmaceutical industry.

How much time will be needed for the interview?

Approximately 45-60 minutes.

What format will the interview take?

The interviews are intended to be relatively informal, on a one-to-one basis and follow a semi-structured question format. With your permission, the interviews will be recorded, as this enables complete and accurate capture of the interview material. The recordings and interview transcripts will be kept in locked storage and will be destroyed on completion of the Ph.D.

I would like to emphasise that all interview data will be anonymised and therefore no comments will be attributed to particular individuals unless authorisation is provided. If you agree to discuss the case study drug, the interview data would be attributable to your company. If there are any issues with this they can be discussed beforehand. I will also feedback a précis of the interview themes so that you will have the opportunity to amend or append as you see fit.

How was your company's drug chosen as a case study?

Through consultation with a group of 11 leading national health care experts, approximately 30 drugs launched in the UK between 1990-2000 were highlighted. Usage data was then obtained from IMS Health for these 30 drugs and converted into daily defined doses to produce diffusion curves. The final case study drugs were then chosen on the basis of them being the class market leader.

What will the research be used for?

The interview data in the first instance will contribute towards the completion of the Ph.D. The aim is to then disseminate the overall findings at conferences and internally within the university. The intention is to also use segments of the Ph.D. to produce papers for peer-reviewed journals.

Appendix 7: Interviewee population: Elite Characteristics

Elites are defined as a small group or class of persons, enjoying superior intellectual, social, or economic status. They possess disproportionately large amounts of influence over political decision making, money, social prestige and political power (Ostrander, 1995; Duke, 2002). The basis of an elite's power is believed to be their knowledge (Hunter, 1995). However, the resulting distortion of the power balance between the elite and the researcher can be advantageously used. According to Walford (1994), Ph.D. students often stand the greatest chance of interviewing elite subjects. Their vulnerable position within the academic research hierarchy, with low status and no significant academic credentials, can mean that access may be easier if the researcher is perceived to be 'harmless', non-threatening and without power.

According to Duke (2002), researching those in positions of power presents a unique set of problems and difficulties, involving access, but also the distortion in the power balance between the researcher and interviewee, which has led to a paucity of research on elites. This lack of knowledge and research on the powerful contributes to mystifying their roles and therefore maintains their position of privilege in society. These sentiments have particular pertinence in the pharmaceutical industry that is commonly safeguarded by clauses of confidentiality.

Gaining access to elites can be problematic as they have the power to create barriers and shield themselves from scrutiny. Access is easier for researchers who have existing links with those in power, and according to Fitz and Halpin (1994), is "contingent and conditional and researchers have to know how to 'play the game'". Elites are often very comfortable with the idea and methods of research and terminology being, in many cases, the holders of higher degrees themselves. This may encourage them however, to be more inclined to co-operate with the research.

A unique situation that confronts researchers of elites is that they can often undergo a process of validation by the respondent. This determines whether the researcher is sufficiently knowledgeable to justify the use of their time and to determine the extent to which they know the field i.e. does the researcher know people they think they should know. Elites are also particularly interested in knowing who else the researcher has spoken to previously in the course of their research (Cookson, 1994; Ostrander, 1995).

The use of the information provided can often cause concern for elites, particularly regarding the publication of the research and their lack of control over this process. Many are preoccupied with which outlets to use for dissemination and whether they would be able to see the results. Duke (2002) mentioned that it is not uncommon for elites to recommend other sources of publication in an attempt to exercise some control. However, the areas of interpretation, dissemination and publication are territories in which the researcher can exert some power and control over elites.

Appendix 8: Timeline Construction - Literature Search

Search terms and sources searched to identify relevant information in the published and 'grey' literature for the purpose of constructing background chapters and timelines for each case study are documented below. The strategy required a broad focus to capture events that may have impacted on the diffusion curve and was adapted and modified from those developed for NIHR Horizon Scanning Centre projects (although the yield of hits was significantly larger as products had been licensed for several years). Electronic search strings were refined in response to emerging data, and pursuing references of references often enabled original documents and original dates of publication to be identified.

1. Search terms from the two columns in Table A8.1 were combined in:
    - Internet search engines (Google/Google Scholar)
    - Medical and economic electronic databases (MEDLINE, EmBASE and EconLit)

2. Searches of specific sources using drug code/name/class and indication included:
    - Drug development databases:
      - PharmaProjects (Informa Healthcare www.pharmaprojects.com)
      - Adis R&D Insight (Springer International Publishing AG www.adisinsight.com)
    - Manufacturer websites/annual reports and ABPI sales information/ trial information and company profiles.
    - Analyst reports
    - NICE - guidelines/ technology appraisals (completed and in development) and stakeholder comments
    - National and international clinical guidelines finder portals (work predated NHS Evidence)
    - Cochrane Library
    - Drug information sources: Regulatory agencies (MHRA/EMA/FDA): Electronic Medicines Compendium; National Prescribing Centre (NPC); UK Medicines Information (UKMi), British National Formulary (BNF).

Table A8.1: Search terms for background case study literature

Case Study Drugs	Timeline Event Keywords
• Drug class name e.g. PDE5 inhibitors OR individual non-proprietary name e.g. sildenafil OR proprietary (trade/brand) name e.g. Viagra OR clinical development code e.g. UK-92480 • Indication e.g. erectile dysfunction	Story OR Stories History Marketing [AND strategy] Review Background Development Timeline Competition Controversy Advertising Blockbusters Overview Launch [AND strategy] Challenges OR Obstacles Clinical [trials OR studies OR evidence] AND: Pivotal Phase III Key Major Influential Landmark Empirical Advertising AND phase III Guidelines Safety Warnings OR Concerns

Methodological issues:

1. Historical guidelines were difficult to find and access once they have been superseded and replaced with current versions.
2. Determining when guidelines were first available as reports, versus when they were published in journals, was often challenging, requiring extensive internet document searches. It was not uncommon for report authors to do spin off publications in specialist journals, in addition to the formal organisational report (e.g. the Erectile Dysfunction Association Guidelines were published in the BMJ by two report co-authors. It is not clear at which point the guidelines would have had the most impact).
3. In the latter stages of the timelines, the impact of online publication of research articles, sometimes several months ahead of their print publication was difficult to assess. Due to the constraints of the timeline representations, dates of printed publication for primary research trials were recorded so as to be consistent with studies conducted before advance online publication became available. However, any conference abstracts/presentations of significance available ahead of publication were also highlighted.

Appendix 9: Interview schedule for the semi-structured interviews

Interview Schedule

Introduction to the project/Recording consent

General:

- What do you think are the most important factors that affect the way a technology is taken up into the market (e.g. trials, guidance etc.)?
- Some people think the emphasis of which factors are important has changed over the last decade (due to new barriers e.g. NICE etc). What are your views on this?
- Can you think of a successful technology - What was key to its success?
- Are there any technologies that performed below expectations – reasons for this? Actions taken to deal with this?
- There is a perception that the larger the company, the more successful the technology (linked to marketing ability). What's your view on this?

Case study discussion (Lifecycle strategies):

Pre-launch/launch

- What was the environment like/types of activities that occurred before launch (e.g. disease awareness campaigns, trial design, government priorities)?
- What was your level of awareness of competitors? – how did that influence your behaviour?
- Talked a little about successful technologies earlier. At what point was the launch of this drug considered to be successful?
- What initial barriers to adoption did you encounter, and how did you overcome them?

Post–launch

- In diffusion research we look for distinct phases. How many distinct phases do you feel are represented in your product's diffusion curve?
- What factors do you feel were most influential in each of the phases you have identified? (marketing/guidance/systematic reviews/cost//trials/market entry timing)?
- Was the shape of the diffusion curve what you had expected? What were the ambitions for the drug, and were they fulfilled? If not, how did you deal with it?
- Were your competitors dealing with the same issues that you were facing? Did they do anything differently (based on company culture/size etc.)?
- How responsive is marketing to sales? Did any one marketing technique stand out from your perspective? How do you ascertain which techniques are most effective? Monitor?

End phase

- Most innovations follow the classic S-shaped diffusion curve that eventually reaches a plateau. How do you know when you have reached that plateau? What did you do to change it?
- If you had to choose one factor that has had the most impact on the uptake and diffusion of this particular drug, what would that be?
- Were there any strategies that did not work as well you had anticipated?

Final

- Is there anything else that we have not covered that you think was important in the diffusion of this drug?

Appendix 10: Framework Analysis - Assignment of Interview Material for the 'Clinical Evidence' Theme to the Iteratively Developed Analytical Categories of the Thematic Framework

Framework 1: Assignment of AA interview material (post-coding)

Interview	Evidence Theme/Subthemes						
	Legitimacy (authority)	Quality	Primary studies				Warnings - safety concerns
				Timing	Rejection/Acceptance	Interpretation/ relevance clinical endpoint	
AA 1		it's not really until you get a full blown publication, if you can in a prestigious journal, that would have the most impact, so, you know, if it was in like the Lancet, the BMJ, the data published in those journals would have more impact than data published in a lesser renowned journal.	I think what we've seen is an increasing importance of things like the robustness of your clinical data, and therefore the strength of the clinical trial programme that you've run, so do you have for example head to head comparators with products already on the market that shows that you have the benefit in clinical effect or health economic value, and that has really increased in importance		efficacy that has to be proven with all drugs, so you have to have clinical data that shows you're efficacious, and clinical data that shows that you're well tolerated as well, but efficacy is probably the one driver across all brands		Risperdal was increasingly being used in elderly patients with psychosis, some of the prescribing was off licence, you know, that the clinicians had just decided to use that, but once Melleril was advised not to be used by the Committee for the Safety of Medicines, a lot of patients were actually switched over to Risperdal.
		The most powerful data is sort of, you know, the early clinical data, so the phase IIIb, particularly if you have randomised head to head, you know, double blinded type data, I mean that's regarded as the most powerful data. The systematic reviews are generally regarded as not quite as robust sometimes, although they can be very useful in terms of gathering lots of different opinions together and forming and overall consensus	The data possibly helped to drive some of it, but I think more of that increase you can see was actually driven by the use in elderly patients, I mean the Csernansky data was very very good data. You probably could have argued that we didn't do enough with it, you know, in terms of promoting the data, because it's very good data. Just limits in terms of marketing spend, you know, Jansen-Cilag would generally have a much lower marketing budget than Lilly for example		we had good effective marketing, that was key in driving the success of the brand. We had to have the clinical data as well, but the marketing activity I think really had more of an emphasis on driving the brand's success. Now I think you can - you still have to invest in the marketing, but unless you have the clinical data to back up the marketing, it's far less effective.		probably the biggest impact on Risperdal negatively was this - the CVAE (cerebrovascular adverse event) warning from the MHRA, that, you know, Risperdal shouldn't really be used in elderly patients, that had quite an immediate impact upon sales. I've not seen anything like it before or since then I don't think, but in terms of like the letter went out from the CSM, and it was literally patients were switched, which, you know, is unusual but it happened very fast.
							What happened here was that there was some studies done with Risperdal and some of the other atypical antipsychotics, which actually suggested that Risperdal probably had some risks as well in elderly patients, it was an independent study. And then what happened was that patients - some of the elderly psychosis patients were switched off Risperdal onto other drugs, so we gained there and then began to lose business here.
AA 2+3	It will depend on the quality of the study and where it's published as to whether we would react to it . You've always got to look….you know we have to present lots of evidence for our products and so we tend to….if we get an individual study that comes out and look at what is the body of evidence that either backs that study up or disagrees with that	quality of the data is absolutely paramount to us for a successful product launch. we have to do placebo for regulatory reasons. Physicians want head to head, how do you compare with other products on the marketplace? If you're lucky enough not to be, you know you're first in class then it's slightly different but quality data is critical	At that time we had no head to head data versus risperidone. The differentiation was against the typical antipsychotics, notably haloperidol which did present some problems in the UK because haloperidol, although the standard of care in the US, is less commonly used in the UK and indeed across much of Europe. So haloperidol was really seen as a proxy for typical antipsychotics and people were left to draw their own conclusions about what that	People go to conferences to get the latest stuff so they definitely take note of what's presented at meetings and you can't beat peer review journal publications.	We take them [weight gain side effects] very seriously because I think they're serious issues and I think again it goes back to the body of evidence, you look at the body of evidence and what does it tell you and it tells you that there are issues with all antipsychotics, atypical antipsychotics, so therefore that's why physical health is a very important debate for us and something we take very, very seriously	I think in the last eighteen months people do have real concerns about the metabolic effects. It is causing people to switch away from olanzapine gradually in schizophrenia, but they've not moved away rapidly because again I think the efficacy is still seen as the most important thing, and the company have done quite a good job in trying to minimise, you know, how the side effects are viewed.	

Interview	Evidence Theme/Subthemes						
	Legitimacy (authority)	Quality	Primary studies				Warnings - safety concerns
				Timing	Rejection/Acceptance	Interpretation/ relevance clinical endpoint	
	study, if it's a one off and there's loads disagreeing with it I probably wouldn't bother with it. If it's one of a series and I think longer term it's going to hurt the brand if we don't respond to it, then we'll go proactive and respond to it		meant against their own personal standard of care. Be that another typical, such as chlorpromazine or against risperidone. But I remember one of the great needs and the great pleas from our sales forces at the time was we need head to head data versus risperidone which we simply didn't have				
		The KOLs tend to be on the advisory boards, they would do more high level, look at the quality of your science, look at the quality of your studies, tell you which ones you should use and how it supports your message and your marketing strategy and then you know the individual psychiatrist, what we would call the more jobbing side, who do the day job, they tend to come to focus groups. (MOVED INTO SEPARATE KOL THEME ONCE THIS BECAME A MAJOR THEME)	we only actually used two or three studies at the time of that launch. The most pivotal of which was the Tollenson data. I recall at the time it was the biggest ever study undertaken on a psychiatric population.			I tell you what happened here, it was safety concerns, we had dear doctor letters, and so did Risperdal. Issues with dementia	
AA 4						I think in psychiatry, I think you would struggle to identify a really ground breaking study that kind of meant people used atypicals instead of typicals, one, because of the nature of the illness and the nature of how clinical trials are done. So when you measure, do a trial for a statin and you are measuring cholesterol, you have your primary outcome measures for that trial will be things that doctors that are prescribing them, totally understand. If I talk about a PANSS scale or a Weinmeres scale or any of those scales they are kind of, not artificial but they are a thing that is done in order to get clinical trial results and not just by the industry but that's how you measure the effectiveness of the drugs. Your jobbing day to day psychiatrist may not really understand exactly what a reduction in PAN score means to a patient unless they are involved in clinical trial work.	

Framework 2: Assignment of AA interview material (post-analysis)

Interview	Evidence Theme/Subthemes								
	Safety			Clinical data		Evidence translation	Policy and guidelines (MOVED INTO EVIDENCE FROM POLICY & GOVERNMENT)		
	Unlicensed use	Regulatory issues	Adverse effects	Primary	Secondary	Relevance of outcomes	Mandatory nature	Differentiation	Timing
AA 1	Risperdal was increasingly being used in elderly patients with psychosis, some of the prescribing was off licence, you know, that the clinicians had just decided to use that, but once Melleril was advised not to be used by the Committee for the Safety of Medicines, a lot of patients were actually switched over to Risperdal.	What happened here was that there was some studies done with Risperdal and some of the other atypical antipsychotics, which actually suggested that Risperdal probably had some risks as well in elderly patients, it was an independent study. And then what happened was that patients - some of the elderly psychosis patients were switched off Risperdal onto other drugs, so we gained there and then began to lose business here		The data possibly helped to drive some of it, but I think more of that increase you can see was actually driven by the use in elderly patients, I mean the Csernansky data was very very good data. You probably could have argued that we didn't do enough with it, you know, in terms of promoting the data, because it's very good data. Just limits in terms of marketing spend, you know, Jansen-Cilag would generally have a much lower marketing budget than Lilly for example.	The most powerful data is sort of, you know, the early clinical data, so the phase IIIb, particularly if you have randomised head to head, you know, double blinded type data, I mean that's regarded as the most powerful data. The systematic reviews are generally regarded as not quite as robust sometimes, although they can be very useful in terms of gathering lots of different opinions together and forming and overall consensus		very strong recommendations from NICE I think, but it depends on the wording and how strong it is, so I think the fact that they were positive about atypicals did have an impact.		
	I mean if people have used it in a certain area and found it works very well, then, you know, once it's licensed they would be inclined to use more of it.			we had good effective marketing, that was key in driving the success of the brand. We had to have the clinical data as well, but the marketing activity I think really had more of an emphasis on driving the brand's success. Now I think you can - you still have to invest in the marketing, but unless you have the clinical data to back up the marketing, it's far less effective.					
	probably the biggest impact on Risperdal negatively was this - the CVAE (cerebrovascular adverse event) warning from the MHRA, that, you know, Risperdal shouldn't really be used in elderly patients, that had quite an immediate impact upon sales. I've not seen anything like it before or since then I don't think, but in terms of like the letter went out from the CSM, and it was literally patients were switched, which, you know, is unusual but it happened very fast.			efficacy that has to be proven with all drugs, so you have to have clinical data that shows you're efficacious, and clinical data that shows that you're well tolerated as well, but efficacy is probably the one driver across all brands					
				I think what we've seen is an increasing importance of things like the robustness of your clinical data, and therefore the strength of the clinical trial programme that you've run, so do you have for example head to head comparators with products already on the market that shows that you have the benefit in clinical effect or health economic value, and that has really increased in					

Interview	Evidence Theme/Subthemes								
	Safety			Clinical data		Evidence translation	Policy and guidelines (MOVED INTO EVIDENCE FROM POLICY & GOVERNMENT)		
	Unlicensed use	Regulatory issues	Adverse effects	Primary	Secondary	Relevance of outcomes	Mandatory nature	Differentiation	Timing
				importance					
				it's not really until you get a full blown publication, if you can in a prestigious journal, that would have the most impact, so, you know, if it was in like the Lancet, the BMJ, the data published in those journals would have more impact than data published in a lesser renowned journal.					
				There's been two big - quite big government studies recently, CATIE and CUTLASS, one in the states and one here, that actually is questioning the value of atypicals, that some people - particularly payers I think - are taking notice of. Psychiatrists I think are more sceptical of the data because they've had the clinical experience and they see a difference. I think most psychiatrists, you know, would say no, I think atypicals are better (MOVED FROM EXPERIENCE THEME INTO EVIDENCE POST-AA ANALYSIS. ON LATER MERGING AAs WITH OTHER CASES IT WAS MOVED BACK TO EXPERIENCE THEME).					
AA 2+3		I tell you what happened here, it was safety concerns, we had dear doctor letters, and so did Risperdal. Issues with dementia	I think in the last eighteen months people do have real concerns about the metabolic effects. It is causing people to switch away from olanzapine gradually in schizophrenia, but they've not moved away rapidly because again I think the efficacy is still seen as the most important thing, and the company have done quite a good job in trying to minimise, you know, how the side effects are viewed.			At that time we had no head to head data versus risperidone. The differentiation was against the typical antipsychotics, notably haloperidol which did present some problems in the UK because haloperidol, although the standard of care in the US, is less commonly used in the UK and indeed across much of Europe. So haloperidol was really seen as a proxy for typical antipsychotics and people were left to draw their own conclusions about what that meant against their own personal standard of care. Be that another typical, such as chlorpromazine or against risperidone. But I remember one of the great needs and the great pleas from our sales forces at the time was we need head to head data versus risperidone which we simply didn't have.	what's the environment like, what are the key priorities in the UK environment, are there government policies and pressures that we can leverage from the communication perspective that says you should…..this is really important to you because the government are asking you to do this and our product will help you do that.	What NICE did do though was say there was a need for atypicals and that from our perspective is a good message. You still have a lot of typical use going on here…they are an advance, atypical antipsychotics, we should be thinking of using them 'cos the older typicals had and still do have very serious side effects, so that message helps us. NICE guidelines that followed the guidance they did differentiate on drugs and olanzapine for instance….was pulled out for crisis in the wards, rapid tranquilisation. And then that way that does help us because you can then actually use that to say like olanzapine has been the drug of choice in this situation	the fact that NICE Guidance was produced relatively late in the lifecycle of Zyprexa meant that impact on people's prescribing habits was probably fairly limited. Had they come along three or four years earlier than they did then it might be a different answer, but they came along so late.
			We take them [weight gain side effects] very seriously because I think they're serious issues and I think again it goes back to the body of	There was such a pent up demand for this drug. And I remember being at some of the congresses where the Phase III data were presented on Zyprexa prior to its launch. And it was standing room only in some of the			NSF not very useful. Lots of best practice and that's what we should do but not a lot to really help the NHS make those changes. Interesting documents to read, you know,		

Interview	Evidence Theme/Subthemes							
	Safety			Clinical data		Evidence translation	Policy and guidelines (MOVED INTO EVIDENCE FROM POLICY & GOVERNMENT)		
	Unlicensed use	Regulatory issues	Adverse effects	Primary	Secondary	Relevance of outcomes	Mandatory nature	Differentiation	Timing
			evidence, you look at the body of evidence and what does it tell you and it tells you that there are issues with all antipsychotics, atypical antipsychotics, so therefore that's why physical health is a very important debate for us and something we take very, very seriously (MOVED FROM REJECTION/ ACCEPTANCE)	auditoria where the data were presented. People really were excited about this. That it did represent a breakthrough (MOVED FROM CLINICAL NEED TO EVIDENCE)			good visions for where they need to be but then you've got to make it happen on the ground haven't you.		
				People go to conferences to get the latest stuff so they definitely take note of what's presented at meetings and you can't beat peer review journal publications.					
				It will depend on the quality of the study and where it's published as to whether we would react to it . You've always got to look….you know we have to present lots of evidence for our products and so we tend to….if we get an individual study that comes out and look at what is the body of evidence that either backs that study up or disagrees with that study, if it's a one off and there's loads disagreeing with it I probably wouldn't bother with it. If it's one of a series and I think longer term it's going to hurt the brand if we don't respond to it, then we'll go proactive and respond to it					
				quality of the data is absolutely paramount to us for a successful product launch. we have to do placebo for regulatory reasons. Physicians want head to head, how do you compare with other products on the marketplace? If you're lucky enough not to be, you know you're first in class then it's slightly different but quality data is critical					
				There was such a pent up demand for this drug. And I remember being at some of the congresses where the Phase III data were presented on Zyprexa prior to its launch. And it was standing room only in some of the auditoria where the data were presented. People really were excited about this. That it did represent a breakthrough (MOVED FROM CLINICAL NEED TO EVIDENCE)					

Interview	Evidence Theme/Subthemes								
	Safety			Clinical data		Evidence translation	Policy and guidelines (MOVED INTO EVIDENCE FROM POLICY & GOVERNMENT)		
	Unlicensed use	Regulatory issues	Adverse effects	Primary	Secondary	Relevance of outcomes	Mandatory nature	Differentiation	Timing
				we only actually used two or three studies at the time of that launch. The most pivotal of which was the Tollenson data. I recall at the time it was the biggest ever study undertaken on a psychiatric population.					
				Evidence will convince somebody or otherwise to give something a go. But at the end of the day there's no substitute for good old fashioned personal clinical experience. By the time it gets to Guidelines people have formed an opinion through their own clinical experience anyway (MOVED FROM EXPERIENCE THEME INTO EVIDENCE POST-AA ANALYSIS. ON LATER MERGING AAs WITH OTHER CASES IT GOT MOVED BACK TO EXPERIENCE THEME)					
AA 4				Regardless of what your clinical data says, doctors don't perceive Seroquel to be as effective as either olanzapine or risperidone. NICE guidance says it is, but our doctors don't believe it, because their experience is Seroquel doesn't work as well. So unless you get them to kind of re-evaluate and use it at the right dose…their perception won't change (MOVED FROM EXPERIENCE THEME INTO EVIDENCE POST AA ANALYSIS. ON LATER MERGING AAs WITH OTHER CASES IT GOT MOVED BACK TO EXPERIENCE THEME)		I think in psychiatry, I think you would struggle to identify a really ground breaking study that kind of meant people used atypicals instead of typicals, one, because of the nature of the illness and the nature of how clinical trials are done. So when you measure, do a trial for a statin and you are measuring cholesterol, you have your primary outcome measures for that trial will be things that doctors that are prescribing them, totally understand. If I talk about a PANSS scale or a Weinmeres scale or any of those scales they are kind of, not artificial but they are a thing that is done in order to get clinical trial results and not just by the industry but that's how you measure the effectiveness of the drugs. Your jobbing day to day psychiatrist may not really understand exactly what a reduction in PAN score means to a patient unless they are involved in clinical trial work.			

Framework 3: Assignment of BP interview material (post-coding)

Interviews	Evidence Theme/Subthemes							
	Safety			Clinical effectiveness (Primary level data)			Evidence translation	
	Unlicensed use	Regulatory issues	Adverse effects		Trial design	Journal quality/publication control	Trial outcomes: planned vs serendipitous	Tailored to adopter category (clinical relevance of outcomes) (MOVED EVENTUALLY TO COMMUNICATION THEME)
BP1		There is genuinely a concern that etidronate as a first generation bisphosphonate, that if you give it in too a higher dose then it causes osteomalacia which is basically malformed bone, so that the bone that it's making is not of a sufficient quality. And we know that, it came out from the sciences, and the solution from a scientific point of view was to give it in cyclical regiment, so that's why it became Didronel PMO [etidronate] and had a cyclical regimen of 14 days of Didronel followed by the calcium, vitamin D…that's all done to stop osteomalacia occurring because in that dosing cycle it doesn't happen. The US have higher concerns about that than the European regulators, so, it's not unusual that different regulators have different concerns. You could, as a company, submit new data to shift the opinion of the regulators, but you reach a point relatively quickly when you get regulatory delay, that because of the intellectual property rights that you have on the product it becomes unviable to bring it to market within the time space you have back to actually recoup your additional costs and your base costs. It went on and got a licence in Europe, but it never managed to get a licence in the US.	it went on and got a licence in Europe, but it never managed to get a licence in US, it had a licence in Canada, the UK and 12 other markets, but not in the US which also means that as an overall opportunity for any company it's lower down the list than something like Actonel [risedronate] which has now got a licence in 83.	I think really the key innovators who are really running the basic science involved in the big clinical trials as lead investigators, they want the next thing, they want to know something new, something that's not been tried with the products, something that's a new indication, a new area, a new formulation, a new piece in the lifecycle management (MOVED EVENTUALLY TO COMMUNICATION THEME)				the innovators and the early adopters might have actually quite low usage but they drive a huge amount of influence to drive acceptance of these as established treatments for the people that follow, so you usually only start to see the pickup when you've got the early adopters and you're into the early majority that's when you see the pick up. So they tend to follow those curves so I think each bit of material has a role to play in how you educate those different groups, because they want to hear something different.
								By the time you've got a peer review publication, or you've got a full systematic review or meta analysis, it's a little bit too late to be taking that information to the people that are your innovators and early adopters. Those are wonderful tools that can actually help address the concerns of the middle majority which tends to be then more in, I would say not highly specialised secondary care or in primary care, in the case of osteoporosis primary care, because that's what they want, and everyone wants something different.
BP2			I think the adverse effect issue for alendronate slowed down the adoption curve, I think you should have seen it rise above that. So I think the fact that	Large scale trials do carry weight but I think the problem is that as soon as they carry some weight they also become the next benchmark.	And at that point we needed to shoot above where MSD were in terms of their studies so they had done BMD, they had done vertebral fracture, they hadn't	We were very heavily focussed on securing a very credible publication for our hip fracture trial published	I think what disappointed us, and I think there's two things, one is fortuitous, I think that the bisphosphonates are a very good class of drugs, so I will be honest	When you're into the early adopters this is where I think it gets really interesting where you're getting into a slightly broader number of again specialists that are shaping and leading the way that the product will be used, and those individuals want to…I think they really are stating to look

Interviews	Evidence Theme/Subthemes							
	Safety			Clinical effectiveness (Primary level data)			Evidence translation	
	Unlicensed use	Regulatory issues	Adverse effects		Trial design	Journal quality/publication control	Trial outcomes: planned vs serendipitous	Tailored to adopter category (clinical relevance of outcomes) (MOVED EVENTUALLY TO COMMUNICATION THEME)
			there was some scepticism in the marketplace about that.		really had hip fracture as a primary end point, but they key element was that we had a hip fracture drug at the primary end point where hip fracture was prospectively planned, and then obviously the study was sizably geared to show that, so you're looking at 10,000 patient plus. But we had 330 investigators, 16,000 patients, 18 countries.	in NEJM and NEJM is still regarded as the highest impact factor publication, out of all the publications you can have. The downside is that they'revery fastidious about how things work, so the first thing is that you can't do the gradual release it has to be brand new to the world, otherwise it never gets into NEJM, and so it puts a lot of blocks on what you can do, because from a marketing point of view, we want to be able to build up to it, but they won't do that, and that's why they're so prestigious.	with you I think they all work, and they're all substantially above what you're basic calcium vitamin D does, so that's the great news for the class yes? The bad news, because they all work, that when you try and plan in 1993 what you're expecting breakthrough to do, which was that we were planning to show a significant reduction in hip fracture that no one else would have, we actually got trumped by Fosamax (alendronate) because they showed fortuitously because it was never powered to show it, they showed fortuitously that they did reduce significantly reduce hip fracture in their trials, because they had a good drug, and we had a good drug, you know, so the reality is that had they not shown hip fracture, had they only ever shown vertebral fracture, which is what we were predicting at the time, then ours, because it was powered to show hip fracture, should have been able to do the bit where it became the market leader.	at congress level activity, abstracts are an indicator of what to watch out for, there may be a couple of things they take home as little gems from that, but they're looking for oral presentations that are interrogating the next level up of influences, and they obviously are interested in making sure that as soon as a peer review publication comes out they've got it,
					Our cost of entry is becoming increasingly higher and the next one is that there's not going to be a head-to-head trial on hip fracture between any drugs, because when they all work as well as all of these do you're talking about 50,000 patients, five years before you even stand a chance of seeing any difference, and when you see the difference it's unlikely to be clinically that significantly and meaningful to actually knock one out of the market and favour the other.	The other element is that they shape the publication, so actually it's from a technical point of view it's not the best written publication, it doesn't do justice to the dataset that supports the publication, but we again don't have a lot of say in that because it's NEJM and they have a lot of say in what they want and how they want it written		
BP 3	There was obviously an opportunity for us to say treat with Alendronate when HRT was no longer recommended in osteoporosis, but our licence was really for treatment, not prevention. And there might be some spill over into doctors that said 'well this patient I can see is going to	Bisphosphonates are not a very nice class of drugs to take. Didronel was a cyclical bisphosphonate so you took the active ingredient for a certain period of time, and then you took calcium for a certain period of time. It was not a very easy thing to take but people were used to doing it. Our once daily came in, we had a fracture intervention trial which came through in publication '96, the FIT	But when you come in and you have an issue of adverse tolerability like this which is causing oesophageal irritation. They're caustic drugs, they're designed in a way, it's a nasty acid but it diffuses once it gets in the gut, but you know, with an elderly population you often get reflux and that can push the acid back into the	Clearly the trial designs that are done for regulatory purposes need to also meet the needs of being able to communicate the benefits of the medicine to the wider community, because you won't have typically in market studies for some years until after the medicine is launched. So you need to have robust data which is going to be able to present to	it's also very important to design those studies in a way where you capture data for socio-economic, health economic cases that you can build for to understand the pricing of the medicine. You know, that's not just done by whim, it's done by a form of science. I mean it is an art, and it's also a measure of the competitiveness of that field, but if			

Interviews	Evidence Theme/Subthemes							
	Safety			Clinical effectiveness (Primary level data)			Evidence translation	
	Unlicensed use	Regulatory issues	Adverse effects		Trial design	Journal quality/publication control	Trial outcomes: planned vs serendipitous	Tailored to adopter category (clinical relevance of outcomes) (MOVED EVENTUALLY TO COMMUNICATION THEME)
	be osteoporotic so I will treat now, and treat early', so our message was only about treat osteoporosis for confirmed osteoporosis cases and not to go after people who were being treated with HRT for menopausal issues. There are other alternatives available for that.	trial, so that gave you the evidence base, it was very quick after launch, and every expectation would have been then that this drug would have flowed because a big population which is under treated, existing therapy not particularly attractive for anybody to take, patient, doctor. But, at the same time as we had this, we did have incidence of adverse tolerability particularly in the United States which lead to a world-wide need for us to write a 'dear doctor' letter. You know, an awareness letter to the doctor saying 'watch out for tolerability'. Well then you see your competition, some will walk away from that, and say 'that's going to be really bad news for growing this market' and some will say 'that's great news, I'll keep my market share', so it depends on whether the motivation of the competitor is market share or market expansion.	oesophagus. And the competition made hay with that. And consequently we got a relatively slow uptake curve, even though we were promoting quite extensively doing a lot of education and advertising, calling on doctors, we couldn't change behaviour because this was the message that they'd got in their head from the competition, and, to be fair, patients were referring…you know, we did have instances where patients were actually reporting this to the doctor	people, regulators, to payers, to physicians, to everybody that actually gives a compelling story of why we would use the drug. So marketing gets involved before launch is what I'm saying.	you're first in the market with a brand new medicine, with a brand new class, how do you price it? You know, you've got to find some means of demonstrating value of the brand and the product to the people who are going to pay for it			
	we were very clear and ethical about this, that if you'd got somebody on HRT who is osteoporotic you've been treating with HRT to treat osteoporosis, then, yes use Alendronate, that's a very good alternative for you. But if you've got somebody on HRT and they're 50 and they're doing this for menopause management it is not appropriate to use Alendronate at that stage. Some doctors would out of their own choice, but it's not what we were saying. And you will see on that chart of adoption of HRT when it does come down there is some change to our growth curve but it's not that dramatic, it's not the driver.	regulators around the world all have different, slightly different nuances on what data they want to see, which makes it expensive to bring a medicine to market, because you can't necessarily use the same file around the world, and that is a frustration through the industry, and it slows access to medicine down. And it costs us money. So that's a frustration, but that's the world that we live in.		Trials get you your position in guidelines. And there are different quality of trials of course. You've got your Phase III regulatory filing, which is against placebo, which just shows the thing works. If it's a highly competitive field, people like to have head-to-head studies versus the leading comparators, or use drugs in the field at the right dose so that they can make a valid judgement call saying 'well this one is better than that one' and they can say they're efficaciously the same but one does this with less side affects and therefore is better pay off for the doctor and the patient. And that will then influence the positioning in the guidelines, so you have to have the trials, the best form of course, which really prove outcomes.	So, you know in the Alendronate case for us it was very important that we had the fracture intervention trial which was published in about 1996. For a big outcomes trial, three year outcomes trial on fracture which really no fracture data of that scale existed in this field before that trial, and to bring that to market less than a year after the launch of the drug was a hugely important thing to do in getting the diffusion of the drug in a very under treated disease. So, that was a good example of a huge …of this designing the trials correctly for Phase III to be extended to produce the outcomes which gives you every argument.			
				you've got to look at the lifecycle of drug development really and say where do certain events come into play? Typically from molecule patenting, registering the molecule which then gives us sort of 20 years of commercial	The interesting facts are in different markets people behave very differently depending on their mindset of whether they're a revenue maximiser or a sales maximiser, and they will design their trials probably to give them a			

Interviews	Evidence Theme/Subthemes							
	Safety			Clinical effectiveness (Primary level data)			Evidence translation	
	Unlicensed use	Regulatory issues	Adverse effects		Trial design	Journal quality/publication control	Trial outcomes: planned vs serendipitous	Tailored to adopter category (clinical relevance of outcomes) (MOVED EVENTUALLY TO COMMUNICATION THEME)
				life, but in the first 10 years of that typically that is just governed by regulatory trials, and safety and efficacy trials. So you're really just trying to find what's the right dose? Does it work and is it safe? And so you're identifying the population in which it will be efficacious in. And that will give you your licence. So typically we've only got 10 years of marketing of the drug when it is actually available for use within whatever population (MOVED TO MARKET PREPARPEDNESS THEME)	predicted result which will fit with that position that they are, their behaviours. As I say, we will typically design everything to try and expand the market to try and get more patients treated (MOVED TO HERITAGE THEME)			
				Fracture discharge, as we would describe it became….that was well-published in all leading journals and has become one of the great case studies in this field. And they're very evidence-based and it was all very evidence-based and so that's why they were preferring to use Alendronate maybe than the competition because they've got the fracture intervention trial plus other evidence, plus the 70 milligram formulation.				
				trials and guidance do influence , well, trials do. Mega trials are very important in terms of getting the opinion leaders to buy into the science quite frankly.				

Framework 4: Assignment of BP interview material (post-analysis)

Interview	Evidence Theme/Subthemes						
	Safety			Clinical effectiveness (primary data)			
	Unlicensed use	Regulatory issues		Trial design	Temporal impact of evidence	Relevance/limitation of trial outcomes	Journal quality/publication control
		Variation in regulatory standards	Adverse effects (official warnings)				
BP1		There is genuinely a concern that etidronate as a first generation bisphosphonate, that if you give it in too a higher dose then it causes osteomalacia which is basically malformed bone, so that the bone that it's making is not of a sufficient quality. And we know that, it came out from the sciences, and the solution from a scientific point of view was to give it in cyclical regiment, so that's why it became Didronel PMO [etidronate] and had a cyclical regimen of 14 days of Didronel followed by the calcium, vitamin D…that's all done to stop osteomalacia occurring because in that dosing cycle it doesn't happen. The US have higher concerns about that than the European regulators, so, it's not unusual that different regulators have different concerns. You could, as a company, submit new data to shift the opinion of the regulators, but you reach a point relatively quickly when you get regulatory delay, that because of the intellectual property rights that you have on the product it becomes unviable to bring it to market within the time space you have back to actually recoup your additional costs and your base costs. It went on and got a licence in Europe, but it never managed to get a licence in the US.					
		it went on and got a licence in Europe, but it never managed to get a licence in US, it had a licence in Canada, the UK and 12 other markets, but not in the US which also means that as an overall opportunity for any company it's lower down the list than something like Actonel [risedronate] which has now got a licence in 83.					
BP2			I think the adverse effect issue for alendronate slowed down the adoption curve, I think you should have seen it rise above that. So I think the fact that there was some scepticism in the marketplace about that.	I think what disappointed us, and I think there's two things, one is fortuitous, I think that the bisphosphonates are a very good class of drugs, so I will be honest with you I think they all work, and they're all substantially above what you're basic calcium vitamin D does, so that's the great news for the class yes? The bad news, because they all work, that when you try and plan in 1993 what you're expecting breakthrough to do, which was that we were planning to show a significant reduction in hip fracture that no one else would have, we actually got trumped by Fosamax		Our cost of entry is becoming increasingly higher and the next one is that there's not going to be a head-to-head trial on hip fracture between any drugs, because when they all work as well as all of these do you're talking about 50,000 patients, five years before you even stand a chance of seeing any difference, and when you see the difference it's unlikely to be clinically that significantly	We were very heavily focussed on securing a very credible publication for our hip fracture trial published in NEJM and NEJM is still regarded as the highest impact factor publication, out of all the publications you can have. The downside is that they're very fastidious about how things work, so the first thing is that you can't do the gradual release it has to be brand new to the world, otherwise it never gets into NEJM, and so it puts a lot of blocks on what you can do, because from a marketing point of view, we want to be able to build up to it, but they won't do that, and that's

Interview	Evidence Theme/Subthemes						
	Safety			Clinical effectiveness (primary data)			
	Unlicensed use	Regulatory issues		Trial design	Temporal impact of evidence	Relevance/limitation of trial outcomes	Journal quality/publication control
		Variation in regulatory standards	Adverse effects (official warnings)				
				(alendronate) because they showed fortuitously because it was never powered to show it, they showed fortuitously that they did reduce significantly reduce hip fracture in their trials, because they had a good drug, and we had a good drug, you know, so the reality is that had they not shown hip fracture, had they only ever shown vertebral fracture, which is what we were predicting at the time, then ours, because it was powered to show hip fracture, should have been able to do the bit where it became the market leader.		and meaningful to actually knock one out of the market and favour the other.	why they're so prestigious.
				And at that point we needed to shoot above where MSD were in terms of their studies so they had done BMD, they had done vertebral fracture, they hadn't really had hip fracture as a primary end point, but they key element was that we had a hip fracture drug at the primary end point where hip fracture was prospectively planned, and then obviously the study was sizably geared to show that, so you're looking at 10,000 patient plus. But we had 330 investigators, 16,000 patients, 18 countries.			The other element is that they shape the publication, so actually it's from a technical point of view it's not the best written publication, it doesn't do justice to the dataset that supports the publication, but we again don't have a lot of say in that because it's NEJM and they have a lot of say in what they want and how they want it written
				Large scale trials do carry weight but I think the problem is that as soon as they carry some weight they also become the next benchmark.			I think we do make mistakes and I think we probably, as a company, we have often maybe jumped a step in terms of dose ranging so we have an issue in the sense that it's not a problem from a clinical point of view, but I have an issue from a trial point of view that our 2.5 milligram arm disappeared out of the trials and so that's not good because you have to explain it, so we should maybe have dealt with that in a different way. We also had an issue that we wanted to do too much in one trial, so what we chose to do was we chose to have an over 80s group, and again a potentially big market, a potentially big unmet need, but we complicated it. So instead of one nice clean crisp message we ended up with sort of 'well I have to explain a few things about my trial before I can now give you my clean crisp message' so it's not so clean and it's not so crisp. And so I think that's maybe our inexperience in…I think a more experienced pharmaceutical company that is doing this day in and day out and has a cookie cutter of 'this is how we launch a drug' they have the experience, you know, and that is a genuine challenge for a company of our size, which is actually how do we keep up the capability in tasks that are infrequent but important? (MOVED FROM COMMUNICATION THEME TO EVIDENCE THEME)
BP3	There was obviously an	regulators around the world all have	Bisphosphonates are not a very nice class of	So, you know in the Alendronate case for us it	Fracture discharge, as we	it's very difficult to do head-to-	

Interview	Evidence Theme/Subthemes						
	Safety			Clinical effectiveness (primary data)			
	Unlicensed use	Regulatory issues		Trial design	Temporal impact of evidence	Relevance/limitation of trial outcomes	Journal quality/publication control
		Variation in regulatory standards	Adverse effects (official warnings)				
	opportunity for us to say treat with Alendronate when HRT was no longer recommended in osteoporosis, but our licence was really for treatment, not prevention. And there might be some spill over into doctors that said 'well this patient I can see is going to be osteoporotic so I will treat now, and treat early', so our message was only about treat osteoporosis for confirmed osteoporosis cases and not to go after people who were being treated with HRT for menopausal issues. There are other alternatives available for that.	different, slightly different nuances on what data they want to see, which makes it expensive to bring a medicine to market, because you can't necessarily use the same file around the world, and that is a frustration through the industry, and it slows access to medicine down. And it costs us money. So that's a frustration, but that's the world that we live in.	drugs to take. Didronel was a cyclical bisphosphonate so you took the active ingredient for a certain period of time, and then you took calcium for a certain period of time. It was not a very easy thing to take but people were used to doing it. Our once daily came in, we had a fracture intervention trial which came through in publication '96, the FIT trial, so that gave you the evidence base, it was very quick after launch, and every expectation would have been then that this drug would have flowed because a big population which is under treated, existing therapy not particularly attractive for anybody to take, patient, doctor. But, at the same time as we had this, we did have incidence of adverse tolerability particularly in the United States which lead to a world-wide need for us to write a 'dear doctor' letter. You know, an awareness letter to the doctor saying 'watch out for tolerability'. Well then you see your competition, some will walk away from that, and say 'that's going to be really bad news for growing this market' and some will say 'that's great news, I'll keep my market share', so it depends on whether the motivation of the competitor is market share or market expansion.	was very important that we had the fracture intervention trial which was published in about 1996. For a big outcomes trial, three year outcomes trial on fracture which really no fracture data of that scale existed in this field before that trial, and to bring that to market less than a year after the launch of the drug was a hugely important thing to do in getting the diffusion of the drug in a very under treated disease. So, that was a good example of a huge …of this designing the trials correctly for Phase III to be extended to produce the outcomes which gives you every argument.	would describe it became….that was well-published in all leading journals and has become one of the great case studies in this field. And they're very evidence-based and it was all very evidence-based and so that's why they were preferring to use Alendronate maybe than the competition because they've got the fracture intervention trial plus other evidence, plus the 70 milligram formulation.	head trials to prove clinical difference versus an existing field in a drug which you need to do a three to six year study, in a massive population to be powered statistically to prove anything. It's extremely difficult. So you've got to find other markers. In this case that's typically done through bone mineral density which you can actually measure at a relatively short phase and see change, and that would be typically what people will do to try and get an edge over each other.	
	we were very clear and ethical about this, that if you'd got somebody on HRT who is osteoporotic you've been treating with HRT to treat osteoporosis, then, yes use Alendronate, that's a very good alternative for you. But if you've got somebody on HRT and they're 50 and they're doing this for menopause management it is not appropriate to use Alendronate at that stage. Some doctors would out of their own choice, but it's not what we were saying. And you will see on that chart of adoption of HRT when it does come down there is some change to our growth curve but it's not that dramatic, it's not the driver.		But when you come in and you have an issue of adverse tolerability like this which is causing oesophageal irritation. They're caustic drugs, they're designed in a way, it's a nasty acid but it diffuses once it gets in the gut, but you know, with an elderly population you often get reflux and that can push the acid back into the oesophagus. And the competition made hay with that. And consequently we got a relatively slow uptake curve, even though we were promoting quite extensively doing a lot of education and advertising, calling on doctors, we couldn't change behaviour because this was the message that they'd got in their head from the competition, and, to be fair, patients were referring…you know, we did have instances where patients were actually reporting this to the doctor	it's also very important to design those studies in a way where you capture data for socio-economic, health economic cases that you can build for to understand the pricing of the medicine. You know, that's not just done by whim, it's done by a form of science. I mean it is an art, and it's also a measure of the competitiveness of that field, but if you're first in the market with a brand new medicine, with a brand new class, how do you price it? You know, you've got to find some means of demonstrating value of the brand and the product to the people who are going to pay for it			
				trials and guidance do influence , well, trials do. Mega trials are very important in terms of getting the opinion leaders to buy into the science quite frankly.			
				Clearly the trial designs that are done for regulatory purposes need to also meet the needs of being able to communicate the benefits of the medicine to the wider			

Interview	Evidence Theme/Subthemes						
	Safety			Clinical effectiveness (primary data)			
	Unlicensed use	Regulatory issues		Trial design	Temporal impact of evidence	Relevance/limitation of trial outcomes	Journal quality/publication control
		Variation in regulatory standards	Adverse effects (official warnings)				
				community, because you won't have typically in market studies for some years until after the medicine is launched. So you need to have robust data which is going to be able to present to people, regulators, to payers, to physicians, to everybody that actually gives a compelling story of why we would use the drug. So marketing gets involved before launch is what I'm saying.			
				Trials get you your position in guidelines. And there are different quality of trials of course. You've got your Phase III regulatory filing, which is against placebo, which just shows the thing works. If it's a highly competitive field, people like to have head-to-head studies versus the leading comparators, or use drugs in the field at the right dose so that they can make a valid judgement call saying 'well this one is better than that one' and they can say they're efficaciously the same but one does this with less side effects and therefore is better pay off for the doctor and the patient. And that will then influence the positioning in the guidelines, so you have to have the trials, the best form of course, which really prove outcomes.			

Framework 5: Assignment of PDE5 interview material to the amalgamated BP and AA Frameworks (post-coding)

Interview	Evidence Theme/Subthemes							
	Safety			Clinical effectiveness (primary data)				Marketing - market revival with new data
	Unlicensed use	Regulation		Trial design	Temporal impact of evidence	Translation: Relevance/limitation of trial outcomes	Journal quality/publication control	
		Variation in regulatory standards	Adverse effects (official warnings)/contraindications					
BP1		There is genuinely a concern that etidronate as a first generation bisphosphonate, that if you give it in too a higher dose then it causes osteomalacia which is basically malformed bone, so that the bone that it's making is not of a sufficient quality. And we know that, it came out from the sciences, and the solution from a scientific point of view was to give it in cyclical regiment, so that's why it became Didronel PMO [etidronate] and had a cyclical regimen of 14 days of Didronel followed by the calcium, vitamin D…that's all done to stop osteomalacia occurring because in that dosing cycle it doesn't happen. The US have higher concerns about that than the European regulators, so, it's not unusual that different regulators have different concerns. You could, as a company, submit new data to shift the opinion of the regulators, but you reach a point relatively quickly when you get regulatory delay, that because of the intellectual property rights that you have on the product it becomes unviable to bring it to market within the time space you have back to actually recoup your additional costs and your base costs. It went on and got a licence in Europe, but it never managed to get a licence in the US.						
		it went on and got a licence in Europe, but it never managed to get a licence in US, it had a licence in Canada, the UK and 12 other markets, but not in the US which also means that as an overall opportunity for any company it's lower down the list than something like Actonel [risedronate] which has now got a licence in 83.						
BP2			I think the adverse effect issue for alendronate slowed down the adoption curve, I think you should have seen it rise above that. So I think the fact that there was some scepticism in the marketplace about that.	I think what disappointed us, and I think there's two things, one is fortuitous, I think that the bisphosphonates are a very good class of drugs, so I will be honest with you I think they all work, and they're all substantially above what you're basic calcium vitamin D does, so that's the great news for the class yes? The bad news, because they all work, that when you try and plan in 1993 what you're expecting breakthrough to do, which was that we were planning to show a significant		Our cost of entry is becoming increasingly higher and the next one is that there's not going to be a head-to-head trial on hip fracture between any drugs, because when they all work as well as all of these do you're talking about 50,000 patients, five years before you even stand a chance of seeing any difference, and when you see the difference it's unlikely to be clinically that	We were very heavily focussed on securing a very credible publication for our hip fracture trial published in NEJM and NEJM is still regarded as the highest impact factor publication, out of all the publications you can have. The downside is that they're very fastidious about how things work, so the first thing is that you can't do the gradual release it has to be brand new to	

Interview	Evidence Theme/Subthemes							
	Safety			Clinical effectiveness (primary data)				Marketing - market revival with new data
	Unlicensed use	Regulation		Trial design	Temporal impact of evidence	Translation: Relevance/limitation of trial outcomes	Journal quality/publication control	
		Variation in regulatory standards	Adverse effects (official warnings)/contraindications					
				reduction in hip fracture that no one else would have, we actually got trumped by Fosamax (alendronate) because they showed fortuitously because it was never powered to show it, they showed fortuitously that they did reduce significantly reduce hip fracture in their trials, because they had a good drug, and we had a good drug, you know, so the reality is that had they not shown hip fracture, had they only ever shown vertebral fracture, which is what we were predicting at the time, then ours, because it was powered to show hip fracture, should have been able to do the bit where it became the market leader.		significantly and meaningful to actually knock one out of the market and favour the other.	the world, otherwise it never gets into NEJM, and so it puts a lot of blocks on what you can do, because from a marketing point of view, we want to be able to build up to it, but they won't do that, and that's why they're so prestigious.	
				And at that point we needed to shoot above where MSD were in terms of their studies so they had done BMD, they had done vertebral fracture, they hadn't really had hip fracture as a primary end point, but they key element was that we had a hip fracture drug at the primary end point where hip fracture was prospectively planned, and then obviously the study was sizably geared to show that, so you're looking at 10,000 patient plus. But we had 330 investigators, 16,000 patients, 18 countries.			The other element is that they shape the publication, so actually it's from a technical point of view it's not the best written publication, it doesn't do justice to the dataset that supports the publication, but we again don't have a lot of say in that because it's NEJM and they have a lot of say in what they want and how they want it written	
				Large scale trials do carry weight but I think the problem is that as soon as they carry some weight they also become the next benchmark.			I think we do make mistakes and I think we probably, as a company, we have often maybe jumped a step in terms of dose ranging so we have an issue in the sense that it's not a problem from a clinical point of view, but I have an issue from a trial point of view that our 2.5 milligram arm disappeared out of the trials and so that's not good because you have to explain it, so we should maybe have dealt with that in a different way. We also had an issue that we wanted to do too much in one trial, so what we chose to do was we chose to have an over 80s group, and again a potentially big market, a potentially big unmet need, but we complicated it. So instead of one nice clean crisp message we ended up with sort of 'well I have to explain a few things about my trial before I can now give you my	

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							clean crisp message' so it's not so clean and it's not so crisp. And so I think that's maybe our inexperience in…I think a more experienced pharmaceutical company that is doing this day in and day out and has a cookie cutter of 'this is how we launch a drug' they have the experience, you know, and that is a genuine challenge for a company of our size, which is actually how do we keep up the capability in tasks that are infrequent but important? (MOVED FROM COMMUNICATION THEME TO EVIDENCE THEME)	
BP3	There was obviously an opportunity for us to say treat with Alendronate when HRT was no longer recommended in osteoporosis, but our licence was really for treatment, not prevention. And there might be some spill over into doctors that said 'well this patient I can see is going to be osteoporotic so I will treat now, and treat early', so our message was only about treat osteoporosis for confirmed osteoporosis cases and not to go after people who were being treated with HRT for menopausal issues. There are other alternatives available for that.	regulators around the world all have different, slightly different nuances on what data they want to see, which makes it expensive to bring a medicine to market, because you can't necessarily use the same file around the world, and that is a frustration through the industry, and it slows access to medicine down. And it costs us money. So that's a frustration, but that's the world that we live in.	Bisphosphonates are not a very nice class of drugs to take. Didronel was a cyclical bisphosphonate so you took the active ingredient for a certain period of time, and then you took calcium for a certain period of time. It was not a very easy thing to take but people were used to doing it. Our once daily came in, we had a fracture intervention trial which came through in publication '96, the FIT trial, so that gave you the evidence base, it was very quick after launch, and every expectation would have been then that this drug would have flowed because a big population which is under treated, existing therapy not particularly attractive for anybody to take, patient, doctor. But, at the same time as we had this, we did have incidence of adverse tolerability particularly in the United States which lead to a world-wide need for us to write a 'dear doctor' letter. You know, an awareness letter to the doctor saying 'watch out for tolerability'. Well then you see your competition, some will walk away from that, and say 'that's going to be really bad news for growing this market' and some will say 'that's great news, I'll keep my market share', so it depends on whether the motivation of the competitor is market share or market expansion.	So, you know in the Alendronate case for us it was very important that we had the fracture intervention trial which was published in about 1996. For a big outcomes trial, three year outcomes trial on fracture which really no fracture data of that scale existed in this field before that trial, and to bring that to market less than a year after the launch of the drug was a hugely important thing to do in getting the diffusion of the drug in a very under treated disease. So, that was a good example of a huge …of this designing the trials correctly for Phase III to be extended to produce the outcomes which gives you every argument.	Fracture discharge, as we would describe it became….that was well-published in all leading journals and has become one of the great case studies in this field. And they're very evidence-based and it was all very evidence-based and so that's why they were preferring to use Alendronate maybe than the competition because they've got the fracture intervention trial plus other evidence, plus the 70 milligram formulation.	it's very difficult to do head-to-head trials to prove clinical difference versus an existing field in a drug which you need to do a three to six year study, in a massive population to be powered statistically to prove anything. It's extremely difficult. So you've got to find other markers. In this case that's typically done through bone mineral density which you can actually measure at a relatively short phase and see change, and that would be typically what people will do to try and get an edge over each other.		Clearly the trial designs that are done for regulatory purposes need to also meet the needs of being able to communicate the benefits of the medicine to the wider community, because you won't have typically in market studies for some years until after the medicine is launched. So you need to have robust data which is going to be able to present to people, regulators, to payers, to physicians, to everybody that actually gives a compelling story of why we would use the drug. So marketing gets involved before launch is what I'm saying (MOVED FROM TRIAL DESIGN WITH EMERGENCE OF THIS NEW EVIDENCE SUBTHEME)
	we were very clear and		But when you come in and you have	it's also very important to design those				

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	ethical about this, that if you'd got somebody on HRT who is osteoporotic you've been treating with HRT to treat osteoporosis, then, yes use Alendronate, that's a very good alternative for you. But if you've got somebody on HRT and they're 50 and they're doing this for menopause management it is not appropriate to use Alendronate at that stage. Some doctors would out of their own choice, but it's not what we were saying. And you will see on that chart of adoption of HRT when it does come down there is some change to our growth curve but it's not that dramatic, it's not the driver.		an issue of adverse tolerability like this which is causing oesophageal irritation. They're caustic drugs, they're designed in a way, it's a nasty acid but it diffuses once it gets in the gut, but you know, with an elderly population you often get reflux and that can push the acid back into the oesophagus. And the competition made hay with that. And consequently we got a relatively slow uptake curve, even though we were promoting quite extensively doing a lot of education and advertising, calling on doctors, we couldn't change behaviour because this was the message that they'd got in their head from the competition, and, to be fair, patients were referring…you know, we did have instances where patients were actually reporting this to the doctor	studies in a way where you capture data for socio-economic, health economic cases that you can build for to understand the pricing of the medicine. You know, that's not just done by whim, it's done by a form of science. I mean it is an art, and it's also a measure of the competitiveness of that field, but if you're first in the market with a brand new medicine, with a brand new class, how do you price it? You know, you've got to find some means of demonstrating value of the brand and the product to the people who are going to pay for it				
				trials and guidance do influence , well, trials do. Mega trials are very important in terms of getting the opinion leaders to buy into the science quite frankly.				
				Clearly the trial designs that are done for regulatory purposes need to also meet the needs of being able to communicate the benefits of the medicine to the wider community, because you won't have typically in market studies for some years until after the medicine is launched. So you need to have robust data which is going to be able to present to people, regulators, to payers, to physicians, to everybody thaat actually gives a compelling story of why we would use the drug. So marketing gets involved before launch is what I'm saying.				
				Trials get you your position in guidelines. And there are different quality of trials of course. You've got your Phase III regulatory filing, which is against placebo, which just shows the thing works. If it's a highly competitive field, people like to have				

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				head-to-head studies versus the leading comparators, or use drugs in the field at the right dose so that they can make a valid judgement call saying 'well this one is better than that one' and they can say they're efficaciously the same but one does this with less side affects and therefore is better pay off for the doctor and the patient. And that will then influence the positioning in the guidelines, so you have to have the trials, the best form of course, which really prove outcomes.				
PDE1			We also wanted to get the message right about how the drug worked because I mean, the fact is it was very, very effective, but there were a couple of very important aspects. One that it was contraindicated with the use of nitrates which are quite common medicines and you know, contraindicated to the point where it was a safety issue if people used them together, that was one thing that we just had to make sure that was clear…and that was a reasonably commonly used medicine for the target group for Viagra..middle aged men basically.	The thing that Pfizer did very well I think was, we studied Viagra in everyone. This is the point, this is where the evidence I think became increasingly important because we could say, here's our data on diabetes, here's our data in spinal cord injury and you know, psychological cases, and no competitor during that period was ever going to have anything like that. It showed its effectiveness, but it also forces people to compete across loads of different areas, which is very difficult for them to do and raises the cost of entry so we were always going to have a very high market share, you know, very early on.				
			I think it was very helpful that it had a nitrate contraindication in some respects, because I think people knew that we'd checked. I mean obviously we are always going to check what the side effect profile is, but you know, as somebody put it to me; somebody pointing out where the iceberg was, meant that you knew how to sail the ship. So think that was very important	If you actually look at the wealth of information out there I think Viagra's got something like, I don't know, five, ten times more clinical papers than we have on the sheer numbers of it. But if you look at our numbers of head-to-head studies versus them and if you looked at, say, preference, although each of the drugs have got some studies or abstracts which show a preference for one of the other, there's probably more out there, both sponsored and independent, which would show a preference for tadalafil. But that hasn't swayed things.				
PDE2				Ever since this point, end of '05, '06, you've then got a whole load of clinical papers that... ever since launch, physicians have been screaming out for comparative evidence. Show us head-to-head. Tell you what, go and look at the evidence base for head-to-heads now. All the companies have done them to one degree or another. And there's only pretty much one company				

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				who are absolutely driving head-to-head studies and that's us. And I think that speaks volumes for where we stand on the medication. You don't have those at launch you have pretty much registration studies which are...we work and here's the reason to care, unique selling point of it.				
				There are a whole load of different preference studies which were being used at the time but they all had methodological problems. So different doses comparing each other and different instructions and all sorts of weird things going on.				
				A [KOL] turned around and said 'Look, if you're going to do a study head-to-head, this is how you would do it for the PDE5s and it should be open label, crossover randomised', you know, on the right doses, comparing relative doses, given the package instructions and not going beyond that. He designed the trial and we went and did it.				
PDE3			It's really, are they on nitrates, yes, well then they can't have a PD5 inhibitor; nope, then they can have a PDE5 inhibitor and any one of them.	No we kind of had our global colleagues trying to make you know, a big new study and we've got to do a whole load of PR about this, I think the initial regulatory submissions, the studies that we used there, they're the best quality evidence, and I think they still really work for us.			I understand you know, the need for peer-review and everything, but then maybe you leave the review of the data until there's a bit more published data on the other two treatments or you know, I don't know, but it was kind of like, yeah, as much as we tried to discuss it with them, because they give you the opportunity to discuss; it kept coming back to the same thing, that's a poster, that's an abstract, it's not peer-reviewed. Essentially they have to be peer-reviewed to make the meeting, but my understanding is that it's not as critical a review process as maybe a preliminary published paper would go through.	I think possibly one of the reasons why we stay down this end of the market is because we don't do as many studies or trials as the other two products, and we all know; it's almost like a self fulfilling thing, we don't do as many because we're not making as much money, but you know we might make more money if we do more studies, so I think it definitely; from a marketing point of view, it really helps, because you can keep saying the same things but bring new data to the package which then makes it sound new and interesting, whereas if you've got old data that you're just sort of re-hashing all the time, you struggle to make something sound new or interesting, so I think clinical data does have a significant affect.
AA1	Risperdal was		probably the biggest impact on	efficacy that has to be proven with all			it's not really until you get a full	The data possibly helped to

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	increasingly being used in elderly patients with psychosis, some of the prescribing was off licence, you know, that the clinicians had just decided to use that, but once Melleril was advised not to be used by the Committee for the Safety of Medicines, a lot of patients were actually switched over to Risperdal.		Risperdal negatively was this - the CVAE (cerebrovascular adverse event) warning from the MHRA, that, you know, Risperdal shouldn't really be used in elderly patients, that had quite an immediate impact upon sales. I've not seen anything like it before or since then I don't think, but in terms of like the letter went out from the CSM, and it was literally patients were switched, which, you know, is unusual but it happened very fast.	drugs, so you have to have clinical data that shows you're efficacious, and clinical data that shows that you're well tolerated as well, but efficacy is probably the one driver across all brands			blown publication, if you can in a prestigious journal, that would have the most impact, so, you know, if it was in like the Lancet, the BMJ, the data published in those journals would have more impact than data published in a lesser renowned journal.	drive some of it, but I think more of that increase you can see was actually driven by the use in elderly patients, I mean the Csernansky data was very very good data. You probably could have argued that we didn't do enough with it, you know, in terms of promoting the data, because it's very good data. Just limits in terms of marketing spend, you know, Jansen-Cilag would generally have a much lower marketing budget than Lilly for example. (MOVED FROM CLINICAL DATA - PRIMARY WITH EMERGENCE OF THIS NEW EVIDENCE SUBTHEME)
	I mean if people have used it in a certain area and found it works very well, then, you know, once it's licensed they would be inclined to use more of it.		What happened here was that there was some studies done with Risperdal and some of the other atypical antipsychotics, which actually suggested that Risperdal probably had some risks as well in elderly patients, it was an independent study. And then what happened was that patients - some of the elderly psychosis patients were switched off Risperdal onto other drugs, so we gained there and then began to lose business here (MOVED FROM REGULATORY WARNING ONCE CATEGORY WAS MERGED WITH ADVERSE EFFECTS)	I think what we've seen is an increasing importance of things like the robustness of your clinical data, and therefore the strength of the clinical trial programme that you've run, so do you have for example head to head comparators with products already on the market that shows that you have the benefit in clinical effect or health economic value, and that has really increased in importance				we had good effective marketing, that was key in driving the success of the brand. We had to have the clinical data as well, but the marketing activity I think really had more of an emphasis on driving the brand's success. Now I think you can - you still have to invest in the marketing, but unless you have the clinical data to back up the marketing, it's far less effective. (MOVED FROM CLINICAL DATA - PRIMARY WITH EMERGENCE OF THIS NEW EVIDENCE SUBTHEME)
				The most powerful data is sort of, you know, the early clinical data, so the phase IIIb, particularly if you have randomised head to head, you know, double blinded type data, I mean that's regarded as the most powerful data. The systematic reviews are generally regarded as not quite as robust sometimes, although they can be very useful in terms of gathering lots of different opinions together and forming and overall consensus (MOVED FROM SECONDARY DATA TO TRIAL DESIGN)				
AA2 +3	tell you what happened		I think in the last eighteen months	we only actually used two or three studies	People go to		It will depend on the quality of the	

Interview	Evidence Theme/Subthemes							
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	Unlicensed use	Regulation		Trial design	Temporal impact of evidence	Translation: Relevance/limitation of trial outcomes	Journal quality/publication control	
		Variation in regulatory standards	Adverse effects (official warnings)/contraindications					
	here, it was safety concerns, we had dear doctor letters, and so did Risperdal. Issues with dementia (MOVED FROM REGULATORY WARNING SUBTHEME TO UNLICENSED USE)		people do have real concerns about the metabolic effects. It is causing people to switch away from olanzapine gradually in schizophrenia, but they've not moved away rapidly because again I think the efficacy is still seen as the most important thing, and the company have done quite a good job in trying to minimise, you know, how the side effects are viewed.	at the time of that launch. The most pivotal of which was the Tollenson data. I recall at the time it was the biggest ever study undertaken on a psychiatric population.	conferences to get the latest stuff so they definitely take note of what's presented at meetings and you can't beat peer review journal publications. (MOVED FROM TRIAL DESIGN)		study and where it's published as to whether we would react to it . You've always got to look….you know we have to present lots of evidence for our products and so we tend to….if we get an individual study that comes out and look at what is the body of evidence that either backs that study up or disagrees with that study, if it's a one off and there's loads disagreeing with it I probably wouldn't bother with it. If it's one of a series and I think longer term it's going to hurt the brand if we don't respond to it, then we'll go proactive and respond to it (MOVED FROM CLINICAL DATA - PRIMARY TO JOURNAL QUALITY FOLLOWING DEVELOPMENT OF THIS SUBTHEME)	
			We take [weight gain side effects] very seriously because I think they're serious issues and I think again it goes back to the body of evidence, you look at the body of evidence and what does it tell you and it tells you that there are issues with all antipsychotics, atypical antipsychotics, so therefore that's why physical health is a very important debate for us and something we take very, very (EVENTUALLY MOVED TO ENVIRONMENT - GUIDELINE TO DEFLECT DRUG ISSUES)	At that time we had no head to head data versus risperidone. The differentiation was against the typical antipsychotics, notably haloperidol which did present some problems in the UK because haloperidol, although the standard of care in the US, is less commonly used in the UK and indeed across much of Europe. So haloperidol was really seen as a proxy for typical antipsychotics and people were left to draw their own conclusions about what that meant against their own personal standard of care. Be that another typical, such as chlorpromazine or against risperidone. But I remember one of the great needs and the great pleas from our sales forces at the time was we need head to head data versus risperidone which we simply didn't have (MOVED TO TRIAL DESIGN FROM CLINICAL DATA - PRIMARY)	There was such a pent up demand for this drug. And I remember being at some of the congresses where the Phase III data were presented on Zyprexa prior to its launch. And it was standing room only in some of the auditoria where the data were presented. People really were excited about this. That it did represent a breakthrough (MOVED FROM CLINICAL DATA - PRIMARY TO TEMPORAL IMPACT)		quality of the data is absolutely paramount to us for a successful product launch. we have to do placebo for regulatory reasons. Physicians want head to head, how do you compare with other products on the marketplace? If you're lucky enough not to be, you know you're first in class then it's slightly different but quality data is critical (MOVED FROM CLINICAL DATA - PRIMARY TO JOURNAL QUALITY FOLLOWING DEVELOPMENT OF THIS SUBTHEME)	
AA4						I think in psychiatry, I think you would struggle to identify a really ground breaking study that kind of meant people used atypicals instead of typicals, one, because of the nature of the illness and the nature of how clinical trials are done. So when you measure, do a trial for a statin and you are measuring cholesterol, you have		

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		Variation in regulatory standards	Adverse effects (official warnings)/contraindications					
						your primary outcome measures for that trial will be things that doctors that are prescribing them, totally understand. If I talk about a PANSS scale or a Weinmeres scale or any of those scales they are kind of, not artificial but they are a thing that is done in order to get clinical trial results and not just by the industry but that's how you measure the effectiveness of the drugs. Your jobbing day to day psychiatrist may not really understand exactly what a reduction in PAN score means to a patient unless they are involved in clinical trial work		

Framework 6: Assignment of PDE5 interview material to the amalgamated BP and AA Frameworks (post-analysis)

Interview	Evidence Theme/Subthemes								
	Safety/Regulation (SUBTHEMES REORGANISED)			Evidence as marketing (RENAMED TO INCORPORATE NEW INSIGHTS - MARKETING SUBTHEME MERGED INTO THIS BROADER CATEGORY)					
	Warnings		Variation in regulatory standards		Trial design	Evidence translation: Relevance/limitation of trial outcomes (RENAMED)		Temporal impact of evidence	Journal quality/publication control
	Unlicensed use	Adverse effects /contraindications				Head to head comparisons	Surrogate markers		
BP1			There is genuinely a concern that etidronate as a first generation bisphosphonate, that if you give it in too a higher dose then it causes osteomalacia which is basically malformed bone, so that the bone that it's making is not of a sufficient quality. And we know that, it came out from the sciences, and the solution from a scientific point of view was to give it in cyclical regiment, so that's why it became Didronel PMO [etidronate] and had a cyclical regimen of 14 days of Didronel followed by the calcium, vitamin D …that's all done to stop osteomalacia occurring because in that dosing cycle it doesn't happen. The US have higher concerns about that than the European regulators, so, it's not unusual that different regulators have different concerns. You could, as a company, submit new data to shift the opinion of the regulators, but you reach a point relatively quickly when you get regulatory delay, that because of the intellectual property rights that you have on the product it becomes unviable to bring it to market within the time space you have back to actually recoup your additional costs and your base costs. It went on and got a licence in Europe, but it never managed to get a licence in the US.					
			it went on and got a licence in Europe, but it never managed to get a licence in US, it had a licence in Canada, the UK and 12 other markets, but not in the US which also means that as an overall opportunity for any company it's lower down the list than something like Actonel [risedronate] which has now got a						

Interview	Evidence Theme/Subthemes								
	Safety/Regulation (SUBTHEMES REORGANISED)			Evidence as marketing (RENAMED TO INCORPORATE NEW INSIGHTS - MARKETING SUBTHEME MERGED INTO THIS BROADER CATEGORY)					
	Warnings		Variation in regulatory standards		Trial design	Evidence translation: Relevance/limitation of trial outcomes (RENAMED)		Temporal impact of evidence	Journal quality/publication control
	Unlicensed use	Adverse effects /contraindications				Head to head comparisons	Surrogate markers		
			licence in 83.						
BP2		I think the adverse effect issue for alendronate slowed down the adoption curve, I think you should have seen it rise above that. So I think the fact that there was some scepticism in the marketplace about that.			I think what disappointed us, and I think there's two things, one is fortuitous, I think that the bisphosphonates are a very good class of drugs, so I will be honest with you I think they all work, and they're all substantially above what you're basic calcium vitamin D does, so that's the great news for the class yes? The bad news, because they all work, that when you try and plan in 1993 what you're expecting breakthrough to do, which was that we were planning to show a significant reduction in hip fracture that no one else would have, we actually got trumped by Fosamax (alendronate) because they showed fortuitously because it was never powered to show it, they showed fortuitously that they did reduce significantly reduce hip fracture in their trials, because they had a good drug, and we had a good drug, you know, so the reality is that had they not shown hip fracture, had they only ever shown vertebral fracture, which is what we were predicting at the time, then ours, because it was powered to show hip fracture, should have been able to do the bit where it became the market leader.	Our cost of entry is becoming increasingly higher and the next one is that there's not going to be a head-to-head trial on hip fracture between any drugs, because when they all work as well as all of these do you're talking about 50,000 patients, five years before you even stand a chance of seeing any difference, and when you see the difference it's unlikely to be clinically that significantly and meaningful to actually knock one out of the market and favour the other.		I think we do make mistakes and I think we probably, as a company, we have often maybe jumped a step in terms of dose ranging so we have an issue in the sense that it's not a problem from a clinical point of view, but I have an issue from a trial point of view that our 2.5 milligram arm disappeared out of the trials and so that's not good because you have to explain it, so we should maybe have dealt with that in a different way. We also had an issue that we wanted to do too much in one trial, so what we chose to do was we chose to have an over 80s group, and again a potentially big market, a potentially big unmet need, but we complicated it. So instead of one nice clean crisp message we ended up with sort of 'well I have to explain a few things about my trial before I can now give you my clean crisp message' so it's not so clean and it's not so crisp. And so I think that's maybe our inexperience in…I think a more experienced pharmaceutical company that is doing this day in and day out and has a cookie cutter of 'this is how we launch a drug' they have the experience, you know, and that is a genuine challenge for a company of our size, which is actually how do we keep up the capab
					And at that point we needed to shoot above where MSD were in terms of their studies so they had done BMD, they had done vertebral fracture, they hadn't really had hip fracture as a primary end point, but they key element was that we had a hip fracture drug at the primary				The other element is that they shape the publication, so actually it's from a technical point of view it's not the best written publication, it doesn't do justice to the dataset that supports the publication, but we again don't have a lot of say in that because it's NEJM and they have a lot of say in what they want and how

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	Warnings		Variation in regulatory standards		Trial design	Evidence translation: Relevance/limitation of trial outcomes (RENAMED)		Temporal impact of evidence	Journal quality/publication control
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					end point where hip fracture was prospectively planned, and then obviously the study was sizably geared to show that, so you're looking at 10,000 patient plus. But we had 330 investigators, 16,000 patients, 18 countries.				they want it written
					Large scale trials do carry weight but I think the problem is that as soon as they carry some weight they also become the next benchmark.				We were very heavily focussed on securing a very credible publication for our hip fracture trial published in NEJM and NEJM is still regarded as the highest impact factor publication, out of all the publications you can have. The downside is that they'revery fastidious about how things work, so the first thing is that you can't do the gradual release it has to be brand new to the world, otherwise it never gets into NEJM, and so it puts a lot of blocks on what you can do, because from a marketing point of view, we want to be able to build up to it, but they won't do that, and that's why they're so prestigious.
BP3	There was obviously an opportunity for us to say treat with Alendronate when HRT was no longer recommended in osteoporosis, but our licence was really for treatment, not prevention. And there might be some spill over into doctors that said 'well this patient I can see is going to be osteoporotic so I will treat now, and treat early', so our message was only about treat osteoporosis for confirmed osteoporosis cases and not to go after people who were being treated with HRT for menopausal issues. There are other alternatives available for that	Bisphosphonates are not a very nice class of drugs to take. Didronel was a cyclical bisphosphonate so you took the active ingredient for a certain period of time, and then you took calcium for a certain period of time. It was not a very easy thing to take but people were used to doing it. Our once daily came in, we had a fracture intervention trial which came through in publication '96, the FIT trial, so that gave you the evidence base, it was very quick after launch, and every expectation would have been then that this drug would have flowed because a big population which is under treated, existing therapy not particularly attractive for	regulators around the world all have different, slightly different nuances on what data they want to see, which makes it expensive to bring a medicine to market, because you can't necessarily use the same file around the world, and that is a frustration through the industry, and it slows access to medicine down. And it costs us money. So that's a frustration, but that's the world that we live in.	Clearly the trial designs that are done for regulatory purposes need to also meet the needs of being able to communicate the benefits of the medicine to the wider community, because you won't have typically in market studies for some years until after the medicine is launched. So you need to have robust data which is going to be able to present to people, regulators, to payers, to physicians, to everybody that actually gives a compelling story of why we would use the drug. So marketing gets involved before launch is what I'm saying	So, you know in the Alendronate case for us it was very important that we had the fracture intervention trial which was published in about 1996. For a big outcomes trial, three year outcomes trial on fracture which really no fracture data of that scale existed in this field before that trial, and to bring that to market less than a year after the launch of the drug was a hugely important thing to do in getting the diffusion of the drug in a very under treated disease. So, that was a good example of a huge ...of this designing the trials correctly for Phase III to be extended to produce the outcomes which gives you every argument.		it's very difficult to do head-to-head trials to prove clinical difference versus an existing field in a drug which you need to do a three to six year study, in a massive population to be powered statistically to prove anything. It's extremely difficult. So you've got to find other markers. In this case that's typically done through bone mineral density which you can actually measure at a relatively short phase and see change, and that would be typically what people will do to try and get an edge over each other (REFINED SUBCATEGORY)	Fracture discharge, as we would describe it became….that was well-published in all leading journals and has become one of the great case studies in this field. And they're very evidence-based and it was all very evidence-based and so that's why they were preferring to use Alendronate maybe than the competition because they've got the fracture intervention trial plus other evidence, plus the 70 milligram formulation.	

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		anybody to take, patient, doctor. But, at the same time as we had this, we did have incidence of adverse tolerability particularly in the United States which lead to a world-wide need for us to write a 'dear doctor' letter. You know, an awareness letter to the doctor saying 'watch out for tolerability'. Well then you see your competition, some will walk away from that, and say 'that's going to be really bad news for growing this market' and some will say 'that's great news, I'll keep my market share', so it depends on whether the motivation of the competitor is market share or market expansion.							
	we were very clear and ethical about this, that if you'd got somebody on HRT who is osteoporotic you've been treating with HRT to treat osteoporosis, then, yes use Alendronate, that's a very good alternative for you. But if you've got somebody on HRT and they're 50 and they're doing this for menopause management it is not appropriate to use Alendronate at that stage. Some doctors would out of their own choice, but it's not what we were saying. And you will see on that chart of adoption of HRT when it does come down there is some change to our growth curve but it's not that dramatic, it's not the driver.	But when you come in and you have an issue of adverse tolerability like this which is causing oesophageal irritation. They're caustic drugs, they're designed in a way, it's a nasty acid but it diffuses once it gets in the gut, but you know, with an elderly population you often get reflux and that can push the acid back into the oesophagus. And the competition made hay with that. And consequently we got a relatively slow uptake curve, even though we were promoting quite extensively doing a lot of education and advertising, calling on doctors, we couldn't change behaviour because this was the message that they'd got in their head from the competition, and, to be fair, patients were referring…you know, we did have instances where patients were actually reporting this to the doctor			it's also very important to design those studies in a way where you capture data for socio-economic, health economic cases that you can build for to understand the pricing of the medicine. You know, that's not just done by whim, it's done by a form of science. I mean it is an art, and it's also a measure of the competitiveness of that field, but if you're first in the market with a brand new medicine, with a brand new class, how do you price it? You know, you've got to find some means of demonstrating value of the brand and the product to the people who are going to pay for it				
					trials and guidance do				

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					influence , well, trials do. Mega trials are very important in terms of getting the opinion leaders to buy into the science quite frankly.				
					Trials get you your position in guidelines. And there are different quality of trials of course. You've got your Phase III regulatory filing, which is against placebo, which just shows the thing works. If it's a highly competitive field, people like to have head-to-head studies versus the leading comparators, or use drugs in the field at the right dose so that they can make a valid judgement call saying 'well this one is better than that one' and they can say they're efficaciously the same but one does this with less side affects and therefore is better pay off for the doctor and the patient. And that will then influence the positioning in the guidelines, so you have to have the trials, the best form of course, which really prove outcomes.				
PDE1		We also wanted to get the message right about how the drug worked because I mean, the fact is it was very, very effective, but there were a couple of very important aspects. One that it was contraindicated with the use of nitrates which are quite common medicines and you know, contraindicated to the point where it was a safety issue if people used them together, that was one thing that we just had to make sure that was clear…and that was a reasonably commonly used medicine for the target group for Viagra..middle aged men			The thing that Pfizer did very well I think was, we studied Viagra in everyone. This is the point, this is where the evidence I think became increasingly important because we could say, here's our data on diabetes, here's our data in spinal cord injury and you know, psychological cases, and no competitor during that period was ever going to have anything like that. It showed its effectiveness, but it also forces people to compete across loads of different areas, which is very difficult for them to do and raises the	If you actually look at the wealth of information out there I think Viagra's got something like, I don't know, five, ten times more clinical papers than we have on the sheer numbers of it. But if you look at our numbers of head-to-head studies versus them and if you looked at, say, preference, although each of the drugs have got some studies or abstracts which show a preference for one of the other, there's probably more out there, both sponsored and independent, which would show a preference for tadalafil. But that hasn't swayed things (MOVED FROM TRIAL DESIGN INTO NEW HEAD TO HEAD			

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		basically.			cost of entry so we were always going to have a very high market share, you know, very early on.	COMPARISON SUBCATEGORY)			
		I think it was very helpful that it had a nitrate contraindication in some respects, because I think people knew that we'd checked. I mean obviously we are always going to check what the side effect profile is, but you know, as somebody put it to me; somebody pointing out where the iceberg was, meant that you knew how to sail the ship. So think that was very important							
PDE2					A [KOL] turned around and said 'Look, if you're going to do a study head-to-head, this is how you would do it for the PDE5s and it should be open label, crossover randomised', you know, on the right doses, comparing relative doses, given the package instructions and not going beyond that. He designed the trial and we went and did it.	There are a whole load of different preference studies which were being used at the time but they all had methodological problems. So different doses comparing each other and different instructions and all sorts of weird things going on (MOVED FROM TRIAL DESIGN INTO NEW HEAD TO HEAD COMPARISON SUBCATEGORY)			
						Ever since this point, end of '05, '06, you've then got a whole load of clinical papers that... ever since launch, physicians have been screaming out for comparative evidence. Show us head-to-head. Tell you what, go and look at the evidence base for head-to-heads now. All the companies have done them to one degree or another. And there's only pretty much one company who are absolutely driving head-to-head studies and that's us. And I think that speaks volumes for where we stand on the medication. You don't have those at launch you have pretty much registration studies which are...we work and here's the reason to care, unique selling point of it (MOVED FROM			

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						TRIAL DESIGN INTO NEW HEAD TO HEAD COMPARISON SUBCATEGORY)			
PDE3		It's really, are they on nitrates, yes, well then they can't have a PD5 inhibitor; nope, then they can have a PDE5 inhibitor and any one of them.		I think possibly one of the reasons why we stay down this end of the market is because we don't do as many studies or trials as the other two products, and we all know; it's almost like a self fulfilling thing, we don't do as many because we're not making as much money, but you know we might make more money if we do more studies, so I think it definitely; from a marketing point of view, it really helps, because you can keep saying the same things but bring new data to the package which then makes it sound new and interesting, whereas if you've got old data that you're just sort of re-hashing all the time, you struggle to make something sound new or interesting, so I think clinical data does have a significant affect. (MOVED FROM MARKETING SUBTHEME INTO THIS BROADER CATEGORY)	No we kind of had our global colleagues trying to make you know, a big new study and we've got to do a whole load of PR about this, I think the initial regulatory submissions, the studies that we used there, they're the best quality evidence, and I think they still really work for us				I understand you know, the need for peer-review and everything, but then maybe you leave the review of the data until there's a bit more published data on the other two treatments or you know, I don't know, but it was kind of like, yeah, as much as we tried to discuss it with them, because they give you the opportunity to discuss; it kept coming back to the same thing, that's a poster, that's an abstract, it's not peer-reviewed. Essentially they have to be peer-reviewed to make the meeting, but my understanding is that it's not as critical a review process as maybe a preliminary published paper would go through.
AA1	Risperdal was increasingly being used in elderly patients with psychosis, some of the prescribing was off licence, you know, that the clinicians had just decided to use that, but once Melleril was advised not to be used by the Committee for the Safety of Medicines, a lot of patients were actually switched over to Risperdal.			The data possibly helped to drive some of it, but I think more of that increase you can see was actually driven by the use in elderly patients, I mean the Csernansky data was very very good data. You probably could have argued that we didn't do enough with it, you know, in terms of promoting the data, because it's very good data. Just limits in terms of marketing spend, you know, Jansen-Cilag would generally have a much lower marketing budget than Lilly for example.	efficacy that has to be proven with all drugs, so you have to have clinical data that shows you're efficacious, and clinical data that shows that you're well tolerated as well, but efficacy is probably the one driver across all brands				it's not really until you get a full blown publication, if you can in a prestigious journal, that would have the most impact, so, you know, if it was in like the Lancet, the BMJ, the data published in those journals would have more impact than data published in a lesser renowned journal.
	What happened here was			we had good effective	The most powerful data is				

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	that there was some studies done with Risperdal and some of the other atypical antipsychotics, which actually suggested that Risperdal probably had some risks as well in elderly patients, it was an independent study. And then what happened was that patients - some of the elderly psychosis patients were switched off Risperdal onto other drugs, so we gained there and then began to lose business here (MOVED FROM ADVERSE EVENTS TO UNLICENSED USE)			marketing, that was key in driving the success of the brand. We had to have the clinical data as well, but the marketing activity I think really had more of an emphasis on driving the brand's success. Now I think you can - you still have to invest in the marketing, but unless you have the clinical data to back up the marketing, it's far less effective	sort of, you know, the early clinical data, so the phase IIIb, particularly if you have randomised head to head, you know, double blinded type data, I mean that's regarded as the most powerful data. The systematic reviews are generally regarded as not quite as robust sometimes, although they can be very useful in terms of gathering lots of different opinions together and forming and overall consensus				
	probably the biggest impact on Risperdal negatively was this - the CVAE (cerebrovascular adverse event) warning from the MHRA, that, you know, Risperdal shouldn't really be used in elderly patients, that had quite an immediate impact upon sales. I've not seen anything like it before or since then I don't think, but in terms of like the letter went out from the CSM, and it was literally patients were switched, which, you know, is unusual but it happened very fast (MOVED FROM ADVERSE EVENTS TO UNLICENSED USE)			I think what we've seen is an increasing importance of things like the robustness of your clinical data, and therefore the strength of the clinical trial programme that you've run, so do you have for example head to head comparators with products already on the market that shows that you have the benefit in clinical effect or health economic value, and that has really increased in importance (MOVED FROM TRIAL DESIGN)					
	I mean if people have used it in a certain area and found it works very well, then, you know, once it's licensed they would be inclined to use more of it.								
AA2 +3	I tell you what happened	I think in the last eighteen		we only actually used two or	quality of the data is	At that time we had no head to		People go to	It will depend on the quality of

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	here, it was safety concerns, we had dear doctor letters, and so did Risperdal. Issues with dementia (MOVED FROM REGULATORY WARNING SUBTHEME TO UNLICENSED USE)	months people do have real concerns about the metabolic effects. It is causing people to switch away from olanzapine gradually in schizophrenia, but they've not moved away rapidly because again I think the efficacy is still seen as the most important thing, and the company have done quite a good job in trying to minimise, you know, how the side effects are viewed.		three studies at the time of that launch. The most pivotal of which was the Tollenson data. I recall at the time it was the biggest ever study undertaken on a psychiatric population	absolutely paramount to us for a successful product launch. we have to do placebo for regulatory reasons. Physicians want head to head, how do you compare with other products on the marketplace? If you're lucky enough not to be, you know you're first in class then it's slightly different but quality data is critical (MOVED FROM JOURNAL QUALITY TO TRIAL DESIGN)	head data versus risperidone. The differentiation was against the typical antipsychotics, notably haloperidol which did present some problems in the UK because haloperidol, although the standard of care in the US, is less commonly used in the UK and indeed across much of Europe. So haloperidol was really seen as a proxy for typical antipsychotics and people were left to draw their own conclusions about what that meant against their own personal standard of care. Be that another typical, such as chlorpromazine or against risperidone. But I remember one of the great needs and the great pleas from our sales forces at the time was we need head to head data versus risperidone which we simply didn't have (MOVED FROM TRIAL DESIGN INTO NEW HEAD TO HEAD COMPARISON SUBCATEGORY)		conferences to get the latest stuff so they definitely take note of what's presented at meetings and you can't beat peer review journal publications.	the study and where it's published as to whether we would react to it . You've always got to look….you know we have to present lots of evidence for our products and so we tend to….if we get an individual study that comes out and look at what is the body of evidence that either backs that study up or disagrees with that study, if it's a one off and there's loads disagreeing with it I probably wouldn't bother with it. If it's one of a series and I think longer term it's going to hurt the brand if we don't respond to it, then we'll go proactive and respond to it.
		We take [weight gain side effects] very seriously because I think they're serious issues and I think again it goes back to the body of evidence, you look at the body of evidence and what does it tell you and it tells you that there are issues with all antipsychotics, atypical antipsychotics, so therefore that's why physical health is a very important debate for us and something we take very, very (EVENTUALLY MOVED TO ENVIRONMENT - GUIDELINE)						There was such a pent up demand for this drug. And I remember being at some of the congresses where the Phase III data were presented on Zyprexa prior to its launch. And it was standing room only in some of the auditoria where the data were presented. People really were excited about this. That it did represent a breakthrough	
		We've got a service that we're now training NHS personnel on how to manage physical health in schizophrenic patients, that's endorsed by all the advocacy groups endorsed by the government and that's taken us a lot of							

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		time and a lot of money but we think that's really important and as we are the market leader we should be leading the way on the other issues that need to be addressed (MOVED TO EVIDENCE - ADVERSE EVENTS FROM THE CULTURAL HERITAGE/ COMPANY PERCEPTION THEME)							
AA4							I think in psychiatry, I think you would struggle to identify a really ground breaking study that kind of meant people used atypicals instead of typicals, one, because of the nature of the illness and the nature of how clinical trials are done. So when you measure, do a trial for a statin and you are measuring cholesterol, you have your primary outcome measures for that trial will be things that doctors that are prescribing them, totally understand. If I talk about a PANSS scale or a Weinmeres scale or any of those scales they are kind of, not artificial but they are a thing that is done in order to get clinical trial results and not just by the industry but that's how you measure the effectiveness of the drugs. Your jobbing day to day psychiatrist may not really understand exactly what a reduction in PAN score means to a patient unless they are involved in clinical trial work. (REFINED SUBCATEGORY)		

Framework 7: Assignment of statin and general interview material to the single emergent framework (post-coding)

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BP1			There is genuinely a concern that etidronate as a first generation bisphosphonate, that if you give it in too a higher dose then it causes osteomalacia which is basically malformed bone, so that the bone that it's making is not of a sufficient quality. And we know that, it came out from the sciences, and the solution from a scientific point of view was to give it in cyclical regiment, so that's why it became Didronel PMO [etidronate] and had a cyclical regimen of 14 days of Didronel followed by the calcium, vitamin D…that's all done to stop osteomalacia occurring because in that dosing cycle it doesn't happen. The US have higher concerns about that than the European regulators, so, it's not unusual that different regulators have different concerns. You could, as a company, submit new data to shift the opinion of the regulators, but you reach a point relatively quickly when you get regulatory delay, that because of the intellectual property rights that you have on the product it becomes unviable to bring it to market within the time space you have back to actually recoup your additional costs and your base costs. It went on and got a licence in Europe, but it never managed to get a licence in the US.						
			it went on and got a licence in Europe, but it never managed to get a licence in US, it had a licence in Canada, the UK and 12 other markets, but not in the US which also means that as an overall opportunity for any company it's lower down the list than something like Actonel [risedronate] which has now got a licence in 83.						

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BP2		I think the adverse effect issue for alendronate slowed down the adoption curve, I think you should have seen it rise above that. So I think the fact that there was some scepticism in the marketplace about that.			I think what disappointed us, and I think there's two things, one is fortuitous, I think that the bisphosphonates are a very good class of drugs, so I will be honest with you I think they all work, and they're all substantially above what you're basic calcium vitamin D does, so that's the great news for the class yes? The bad news, because they all work, that when you try and plan in 1993 what you're expecting breakthrough to do, which was that we were planning to show a significant reduction in hip fracture that no one else would have, we actually got trumped by Fosamax (alendronate) because they showed fortuitously because it was never powered to show it, they showed fortuitously that they did reduce significantly reduce hip fracture in their trials, because they had a good drug, and we had a good drug, you know, so the reality is that had they not shown hip fracture, had they only ever shown vertebral fracture, which is what we were predicting at the time, then ours, because it was powered to show hip fracture, should have been able to do the bit where it became the market leader.	Our cost of entry is becoming increasingly higher and the next one is that there's not going to be a head-to-head trial on hip fracture between any drugs, because when they all work as well as all of these do you're talking about 50,000 patients, five years before you even stand a chance of seeing any difference, and when you see the difference it's unlikely to be clinically that significantly and meaningful to actually knock one out of the market and favour the other.			I think we do make mistakes and I think we probably, as a company, we have often maybe jumped a step in terms of dose ranging so we have an issue in the sense that it's not a problem from a clinical point of view, but I have an issue from a trial point of view that our 2.5 milligram arm disappeared out of the trials and so that's not good because you have to explain it, so we should maybe have dealt with that in a different way. We also had an issue that we wanted to do too much in one trial, so what we chose to do was we chose to have an over 80s group, and again a potentially big market, a potentially big unmet need, but we complicated it. So instead of one nice clean crisp message we ended up with sort of 'well I have to explain a few things about my trial before I can now give you my clean crisp message' so it's not so clean and it's not so crisp. And so I think that's maybe our inexperience in…I think a more experienced pharmaceutical company that is doing this day in and day out and has a cookie cutter of 'this is how we launch a drug' they have the experience, you know, and that is a genuine challenge for a company of our size, which is actually how do we keep up the capab
					And at that point we needed to shoot above where MSD were in terms of their studies so they had done BMD, they had done vertebral fracture, they hadn't really had hip fracture as a primary end point, but they key element was that we had a hip fracture drug at the primary end point where hip fracture was prospectively				The other element is that they shape the publication, so actually it's from a technical point of view it's not the best written publication, it doesn't do justice to the dataset that supports the publication, but we again don't have a lot of say in that because it's NEJM and they have a lot of say in what they want and how they

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					planned, and then obviously the study was sizably geared to show that, so you're looking at 10,000 patient plus. But we had 330 investigators, 16,000 patients, 18 countries.				want it written
					Large scale trials do carry weight but I think the problem is that as soon as they carry some weight they also become the next benchmark.				We were very heavily focussed on securing a very credible publication for our hip fracture trial published in NEJM and NEJM is still regarded as the highest impact factor publication, out of all the publications you can have. The downside is that they'revery fastidious about how things work, so the first thing is that you can't do the gradual release it has to be brand new to the world, otherwise it never gets into NEJM, and so it puts a lot of blocks on what you can do, because from a marketing point of view, we want to be able to build up to it, but they won't do that, and that's why they're so prestigious.
BP3	There was obviously an opportunity for us to say treat with Alendronate when HRT was no longer recommended in osteoporosis, but our licence was really for treatment, not prevention. And there might be some spill over into doctors that said 'well this patient I can see is going to be osteoporotic so I will treat now, and treat early', so our message was only about treat osteoporosis for confirmed osteoporosis cases and not to go after people who were being treated with HRT for menopausal issues. There are other alternatives available for that	Bisphosphonates are not a very nice class of drugs to take. Didronel was a cyclical bisphosphonate so you took the active ingredient for a certain period of time, and then you took calcium for a certain period of time. It was not a very easy thing to take but people were used to doing it. Our once daily came in, we had a fracture intervention trial which came through in publication '96, the FIT trial, so that gave you the evidence base, it was very quick after launch, and every expectation would have been then that this drug would have flowed because a big population which is under treated,	regulators around the world all have different, slightly different nuances on what data they want to see, which makes it expensive to bring a medicine to market, because you can't necessarily use the same file around the world, and that is a frustration through the industry, and it slows access to medicine down. And it costs us money. So that's a frustration, but that's the world that we live in.	Clearly the trial designs that are done for regulatory purposes need to also meet the needs of being able to communicate the benefits of the medicine to the wider community, because you won't have typically in market studies for some years until after the medicine is launched. So you need to have robust data which is going to be able to present to people, regulators, to payers, to physicians, to everybody that actually gives a compelling story of why we would use the drug. So marketing gets involved before launch is what I'm saying	So, you know in the Alendronate case for us it was very important that we had the fracture intervention trial which was published in about 1996. For a big outcomes trial, three year outcomes trial on fracture which really no fracture data of that scale existed in this field before that trial, and to bring that to market less than a year after the launch of the drug was a hugely important thing to do in getting the diffusion of the drug in a very under treated disease. So, that was a good example of a huge …of this designing the trials correctly for Phase III to be extended to produce the outcomes which gives you every argument.		it's very difficult to do head-to-head trials to prove clinical difference versus an existing field in a drug which you need to do a three to six year study, in a massive population to be powered statistically to prove anything. It's extremely difficult. So you've got to find other markers. In this case that's typically done through bone mineral density which you can actually measure at a relatively short phase and see change, and that would be typically what people will do to try and get an edge over each other.	Fracture discharge, as we would describe it became….that was well-published in all leading journals and has become one of the great case studies in this field. And they're very evidence-based and it was all very evidence-based and so that's why they were preferring to use Alendronate maybe than the competition because they've got the fracture intervention trial plus other evidence, plus the 70 milligram formulation.	

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		existing therapy not particularly attractive for anybody to take, patient, doctor. But, at the same time as we had this, we did have incidence of adverse tolerability particularly in the United States which lead to a world-wide need for us to write a 'dear doctor' letter. You know, an awareness letter to the doctor saying 'watch out for tolerability'. Well then you see your competition, some will walk away from that, and say 'that's going to be really bad news for growing this market' and some will say 'that's great news, I'll keep my market share', so it depends on whether the motivation of the competitor is market share or market expansion.							
	we were very clear and ethical about this, that if you'd got somebody on HRT who is osteoporotic you've been treating with HRT to treat osteoporosis, then, yes use Alendronate, that's a very good alternative for you. But if you've got somebody on HRT and they're 50 and they're doing this for menopause management it is not appropriate to use Alendronate at that stage. Some doctors would out of their own choice, but it's not what we were saying. And you will see on that chart of adoption of HRT when it does come down there is some change to our growth curve but it's not that dramatic, it's not the driver.	But when you come in and you have an issue of adverse tolerability like this which is causing oesophageal irritation. They're caustic drugs, they're designed in a way, it's a nasty acid but it diffuses once it gets in the gut, but you know, with an elderly population you often get reflux and that can push the acid back into the oesophagus. And the competition made hay with that. And consequently we got a relatively slow uptake curve, even though we were promoting quite extensively doing a lot of education and advertising, calling on doctors, we couldn't change behaviour because this was the message that they'd got in their head from the competition, and, to be fair, patients were			it's also very important to design those studies in a way where you capture data for socio-economic, health economic cases that you can build for to understand the pricing of the medicine. You know, that's not just done by whim, it's done by a form of science. I mean it is an art, and it's also a measure of the competitiveness of that field, but if you're first in the market with a brand new medicine, with a brand new class, how do you price it? You know, you've got to find some means of demonstrating value of the brand and the product to the people who are going to pay for it				

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		referring…you know, we did have instances where patients were actually reporting this to the doctor							
					trials and guidance do influence , well, trials do. Mega trials are very important in terms of getting the opinion leaders to buy into the science quite frankly.				
					Trials get you your position in guidelines. And there are different quality of trials of course. You've got your Phase III regulatory filing, which is against placebo, which just shows the thing works. If it's a highly competitive field, people like to have head-to-head studies versus the leading comparators, or use drugs in the field at the right dose so that they can make a valid judgement call saying 'well this one is better than that one' and they can say they're efficaciously the same but one does this with less side affects and therefore is better pay off for the doctor and the patient. And that will then influence the positioning in the guidelines, so you have to have the trials, the best form of course, which really prove outcomes.				
PDE1		We also wanted to get the message right about how the drug worked because I mean, the fact is it was very, very effective, but there were a couple of very important aspects. One that it was contraindicated with the use of nitrates which are quite common medicines and you know, contraindicated to the point where it was a safety issue if people used them together, that was one			The thing that Pfizer did very well I think was, we studied Viagra in everyone. This is the point, this is where the evidence I think became increasingly important because we could say, here's our data on diabetes, here's our data in spinal cord injury and you know, psychological cases, and no competitor during that period was ever going to have anything like that. It showed its effectiveness, but it also	If you actually look at the wealth of information out there I think Viagra's got something like, I don't know, five, ten times more clinical papers than we have on the sheer numbers of it. But if you look at our numbers of head-to-head studies versus them and if you looked at, say, preference, although each of the drugs have got some studies or abstracts which show a preference for one of the other, there's probably more out there, both sponsored and independent, which would show a preference for tadalafil. But that hasn't swayed things.			

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		thing that we just had to make sure that was clear…and that was a reasonably commonly used medicine for the target group for Viagra..middle aged men basically.			forces people to compete across loads of different areas, which is very difficult for them to do and raises the cost of entry so we were always going to have a very high market share, you know, very early on.				
		I think it was very helpful that it had a nitrate contraindication in some respects, because I think people knew that we'd checked. I mean obviously we are always going to check what the side effect profile is, but you know, as somebody put it to me; somebody pointing out where the iceberg was, meant that you knew how to sail the ship. So think that was very important							
PDE2					A [KOL] turned around and said 'Look, if you're going to do a study head-to-head, this is how you would do it for the PDE5s and it should be open label, crossover randomised', you know, on the right doses, comparing relative doses, given the package instructions and not going beyond that. He designed the trial and we went and did it.	There are a whole load of different preference studies which were being used at the time but they all had methodological problems. So different doses comparing each other and different instructions and all sorts of weird things going on.			
						Ever since this point, end of '05, '06, you've then got a whole load of clinical papers that... ever since launch, physicians have been screaming out for comparative evidence. Show us head-to-head. Tell you what, go and look at the evidence base for head-to-heads now. All the companies have done them to one degree or another. And there's only pretty much one company who are absolutely driving head-to-head studies and that's us. And I think that speaks volumes for where we stand on the medication. You don't have those at launch you have pretty much registration studies which are...we work			

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						and here's the reason to care, unique selling point of it.			
PDE3		It's really, are they on nitrates, yes, well then they can't have a PD5 inhibitor; nope, then they can have a PDE5 inhibitor and any one of them.		I think possibly one of the reasons why we stay down this end of the market is because we don't do as many studies or trials as the other two products, and we all know; it's almost like a self fulfilling thing, we don't do as many because we're not making as much money, but you know we might make more money if we do more studies, so I think it definitely; from a marketing point of view, it really helps, because you can keep saying the same things but bring new data to the package which then makes it sound new and interesting, whereas if you've got old data that you're just sort of re-hashing all the time, you struggle to make something sound new or interesting, so I think clinical data does have a significant affect.	No we kind of had our global colleagues trying to make you know, a big new study and we've got to do a whole load of PR about this, I think the initial regulatory submissions, the studies that we used there, they're the best quality evidence, and I think they still really work for us				I understand you know, the need for peer-review and everything, but then maybe you leave the review of the data until there's a bit more published data on the other two treatments or you know, I don't know, but it was kind of like, yeah, as much as we tried to discuss it with them, because they give you the opportunity to discuss; it kept coming back to the same thing, that's a poster, that's an abstract, it's not peer-reviewed. Essentially they have to be peer-reviewed to make the meeting, but my understanding is that it's not as critical a review process as maybe a preliminary published paper would go through.
AA1	Risperdal was increasingly being used in elderly patients with psychosis, some of the prescribing was off licence, you know, that the clinicians had just decided to use that, but once Melleril was advised not to be used by the Committee for the Safety of Medicines, a lot of patients were actually switched over to Risperdal.			The data possibly helped to drive some of it, but I think more of that increase you can see was actually driven by the use in elderly patients, I mean the Csernansky data was very very good data. You probably could have argued that we didn't do enough with it, you know, in terms of promoting the data, because it's very good data. Just limits in terms of marketing spend, you know, Jansen-Cilag would generally have a much lower marketing budget than Lilly for example.	efficacy that has to be proven with all drugs, so you have to have clinical data that shows you're efficacious, and clinical data that shows that you're well tolerated as well, but efficacy is probably the one driver across all brands				it's not really until you get a full blown publication, if you can in a prestigious journal, that would have the most impact, so, you know, if it was in like the Lancet, the BMJ, the data published in those journals would have more impact than data published in a lesser renowned journal.
	What happened here was that there was some studies done with Risperdal and some of the other atypical antipsychotics, which actually suggested that			we had good effective marketing, that was key in driving the success of the brand. We had to have the clinical data as well, but the marketing activity I think really had more of an emphasis on	The most powerful data is sort of, you know, the early clinical data, so the phase IIIb, particularly if you have randomised head to head, you know, double blinded type data, I mean that's regarded				

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	Risperdal probably had some risks as well in elderly patients, it was an independent study. And then what happened was that patients - some of the elderly psychosis patients were switched off Risperdal onto other drugs, so we gained there and then began to lose business here.			driving the brand's success. Now I think you can - you still have to invest in the marketing, but unless you have the clinical data to back up the marketing, it's far less effective	as the most powerful data. The systematic reviews are generally regarded as not quite as robust sometimes, although they can be very useful in terms of gathering lots of different opinions together and forming and overall consensus				
	probably the biggest impact on Risperdal negatively was this - the CVAE (cerebrovascular adverse event) warning from the MHRA, that, you know, Risperdal shouldn't really be used in elderly patients, that had quite an immediate impact upon sales. I've not seen anything like it before or since then I don't think, but in terms of like the letter went out from the CSM, and it was literally patients were switched, which, you know, is unusual but it happened very fast.			I think what we've seen is an increasing importance of things like the robustness of your clinical data, and therefore the strength of the clinical trial programme that you've run, so do you have for example head to head comparators with products already on the market that shows that you have the benefit in clinical effect or health economic value, and that has really increased in importance.					
	I mean if people have used it in a certain area and found it works very well, then, you know, once it's licensed they would be inclined to use more of it.								
AA2 +3	I tell you what happened here, it was safety concerns, we had dear doctor letters, and so did Risperdal. Issues with dementia.	I think in the last eighteen months people do have real concerns about the metabolic effects. It is causing people to switch away from olanzapine gradually in schizophrenia, but they've not moved away rapidly because again I think the efficacy is still seen as the most important thing, and the company have done quite a good job in trying to		we only actually used two or three studies at the time of that launch. The most pivotal of which was the Tollenson data. I recall at the time it was the biggest ever study undertaken on a psychiatric population	quality of the data is absolutely paramount to us for a successful product launch. we have to do placebo for regulatory reasons. Physicians want head to head, how do you compare with other products on the marketplace? If you're lucky enough not to be, you know you're first in class then it's slightly different but quality data is critical.	At that time we had no head to head data versus risperidone. The differentiation was against the typical antipsychotics, notably haloperidol which did present some problems in the UK because haloperidol, although the standard of care in the US, is less commonly used in the UK and indeed across much of Europe. So haloperidol was really seen as a proxy for typical antipsychotics and people were left to draw their own conclusions about what that meant against their own personal standard of care. Be that another		People go to conferences to get the latest stuff so they definitely take note of what's presented at meetings and you can't beat peer review journal publications.	It will depend on the quality of the study and where it's published as to whether we would react to it . You've always got to look....you know we have to present lots of evidence for our products and so we tend to....if we get an individual study that comes out and look at what is the body of evidence that either backs that study up or disagrees with that study, if it's a one off and there's loads

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		minimise, you know, how the side effects are viewed.				typical, such as chlorpromazine or against risperidone. But I remember one of the great needs and the great pleas from our sales forces at the time was we need head to head data versus risperidone which we simply didn't have.			disagreeing with it I probably wouldn't bother with it. If it's one of a series and I think longer term it's going to hurt the brand if we don't respond to it, then we'll go proactive and respond to it.
		We take them [weight gain side effects] very seriously because I think they're serious issues and I think again it goes back to the body of evidence, you look at the body of evidence and what does it tell you and it tells you that there are issues with all antipsychotics, atypical antipsychotics, so therefore that's why physical health is a very important debate for us and something we take very, very seriously.						There was such a pent up demand for this drug. And I remember being at some of the congresses where the Phase III data were presented on Zyprexa prior to its launch. And it was standing room only in some of the auditoria where the data were presented. People really were excited about this. That it did represent a breakthrough	
		We've got a service that we're now training NHS personnel on how to manage physical health in schizophrenic patients, that's endorsed by all the advocacy groups endorsed by the government and that's taken us a lot of time and a lot of money but we think that's really important and as we are the market leader we should be leading the way on the other issues that need to be addressed							

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AA4							I think in psychiatry, I think you would struggle to identify a really ground breaking study that kind of meant people used atypicals instead of typicals, one, because of the nature of the illness and the nature of how clinical trials are done. So when you measure, do a trial for a statin and you are measuring cholesterol, you have your primary outcome measures for that trial will be things that doctors that are prescribing them, totally understand. If I talk about a PANSS scale or a Weinmeres scale or any of those scales they are kind of, not artificial but they are a thing that is done in order to get clinical trial results and not just by the industry but that's how you measure the effectiveness of the drugs. Your jobbing day to day psychiatrist may not really understand exactly what a reduction in PAN score means to a patient unless they are involved in clinical trial work.		
Statin1					What was going to change the cholesterol lowering market was big trials. If ever there was an area that is characterised by there having been an impact of big randomised controlled trials, it's this area, so I think it was 1994 that the first sort of big landmark study came out, the 4S study, and there for the first time was a demonstrated impact on total mortality, not cardiovascular mortality, but total mortality in a population of middle aged men with existing heart disease and I think that was the turning point at which erm people started to really kind of, sit up and take notice. I mean there had been pretty good evidence	MSD staked their place as market leader for many years really with the 4S trial; they had what was probably of the available statins, the most effective lipid lowerer and they had the evidence to say this drug saves lives and I think , that's reflected in their usage relative to the others. The other drugs were either later or less convincing with their trials, so there was actually very good evidence for Pravastatin, but Pravastatin probably published more landmark trials, through the nineties than Merck did behind Simvastatin, but the drug was less effective at lowering cholesterol and it was the most effective drug in the market place that benefitted.		We've almost got to the point of there being just sheer overkill on the amount of data, I mean how much more evidence do you need that lowering cholesterol saves lives, and there's not much, not many questions left to ask now really.	

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					beforehand, but not in such a simple, elegantly designed, big trial as happened then and I think you really start to see from the back end of '94 that things really start to take off				
Statin2	Pre-launch there's the withdrawal of Cerevastatin which affects the whole statin market in terms of safety profile. The first dynamic phase, was expected because the drugs available weren't controlling the lipids so well I guess. And we had a low dose statin that was able to control lipids easily. These two phases here are caused by Dear Doctor letters which wrote out saying that the dose of rosuvastatin needs to be watched in certain groups of patients. So that was unexpected. And then you look at this phase where obviously you'd expect it to go exponential, it's tapered off a little bit but it has grown. So expected, unexpected, slightly disappointing.	To have two [Dear Doctor letters] was unprecedented to be honest with you, and to recover from two has been a massive success. You've got to add in competitors and how they use it and so obviously they'll use it negatively against you and positively against them. So you have to really get your positive message out into the market one way or another. Whether that's through sales force or it's through meetings, through a combination of both really.			It's a very highly regulated industry in terms of what you can and what you can't present to clinicians. We can convey the results of clinical studies and you can say that that's marketing, you can say that that's science. But I think there's a case to say that it's…certainly in the UK it's, it's pretty difficult to over market a drug just because of the level of regulation. It's that relationship between regulation and marketing and some of the sign off procedures that we have to go through internally such that the representatives can actually share the material with a physician are kind of ludicrous but it's there to protect the industry and the clinicians.			There's not much more evidence you can collect really because most of it's been done in terms of placebo controlled trials, most of it's been done now. It's mostly unethical to do the trials anymore. So we're stuck. So doing more and more trials is probably not the answer, pharmacoeconomics is the answer I think. Make sure that your product is pharmacoeconomically positioned to take advantage of the health system as it is now	
		I think if we hadn't had these Dear Doctor letters this gap here shows you the evidence is not that important. It is now because this happened and people want to see evidence, so if you start it again here, you'd say yes some of the trials have been important but during that first dynamic phase evidence wasn't important to us. Everyone had bought into the fact that lowering LDL is good for you.							

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		Well, I think there wouldn't have been much different at all if the Dear Doctor letters, it would have been straight up until probably Simvastatin came off patent and then we'd be in a similar position to Pfizer, losing a lot of market share							
		When the Dear Doc letters came out in some ways there was a programme of meetings to sort of say, you know, don't worry about it. I often do wonder if the fact that you say to someone don't worry, they worry more. Like don't worry about flying, the first thing you do is like it's going to crash. I think that maybe was a mistake to go so passionately across the country saying don't worry, it's alright. It might have just been better just to say carry on almost as normal and say yeah, we're a statin, we do have side effects, but they're in line with all the rest of those in the class.							
Statin3	When rosuvastatin was first being used, it perhaps wasn't being used appropriately by clinicians. They'd been used to using simvastatin and atorvastatin for however many years at kind of reasonably high doses, 20s and 40s, and they were using rosuvastatin in the same way despite the starting dose being 10mg. And they were actually four cases of rhabdomyolysis associated with starting patients on higher doses of rosuva than there should have been which prompted a letter from the regulatory	Following the launch of Ceriva there was less willingness to treat the statins as a class. There was more of a requirement, much more need in the marketplace to demonstrate long-term safety and that's still something that we're having discussions with clinicians around now it's been on the market for five years in the UK, six years in some markets, has rosuva kind of got that wealth of experience and patient experience required for the physicians to feel comfortable enough to use				I guess the main one, the one that is mostly used within the marketing is the STELLAR trial where the endpoints are cholesterol markers and mainly because it's comparative data across the statins, it's head to head data. A lot of the trials are not head to head but it's possible to do that on cholesterol… when we get our outcomes data then the focus would switch a bit, it's true what we've been telling you, a reduction in cholesterol and it has an event and outcomes benefit.	You have to really ask the question do you believe that it's an LDL story or not? So from 4S onwards every single statin trial that's come out has shown that lowering LDL cholesterol is beneficial. So are you saying that one statin is a miracle drug, or are you saying it's really largely its ability to lower LDL cholesterol? Now if you look at all them together and say okay, then you have the ileal bypass trial, POSCH, which saved lives without any statins, by lowering LDL cholesterol. You have the Cholestepol trials which saved lives by lowering cholesterol.	There was awareness of the clinical data before launch and that it looked fairly strong. Other things that were in place like the QOF which physicians were starting to get wind of which directly incentivises them to go and find patients who were eligible for statin therapy and to treat them to a certain level, those two things together, that's some of the reason behind that.	

Interview	Evidence Theme/Subthemes								
	Safety/Regulation			Evidence as marketing					
	Warnings		Variation in regulatory standards		Trial design	Evidence translation: Relevance/limitation of trial outcomes		Temporal impact of evidence	Journal quality/publication control
	Unlicensed use	Adverse effects /contraindications				Head to head comparisons	Surrogate markers		
	authorities to remind prescribers that the starting dose was 10mg. And so once you send a letter from regulators and with what looks to be a safety concern then that's going to have an impact…looking at what's happened since I think probably statistically it was quite unlucky to have had four in that time frame.	it? And it harks back to things like cerivastatin where people got their fingers burnt. And at the same time, kind of 2004, you had the withdrawal of Vioxx and various other kinds of scares, so for rosuvastatin being a new entrant into a market where there'd already been scares that definitely has an impact on diffusion.					And so if you draw a line from the top to the bottom, you can plot all these trials on a line that basically shows you the lower the LDL cholesterol the better your outcome is. So that's your surrogate market argument. We can lower LDL cholesterol, we can prove it does things to atherosclerosis.		
		I think cerivastatin came to the market claiming superior efficacy and gets withdrawn. Effectively rosuvastatin had to kind of try and do something similar, new statin to the market, proven superior efficacy in order to get usage, definitely had an impact. What you have to do is to show the safety data and say look here's the adverse event reporting data, you can see rosuvastatin is in line with the other statins and cerivastatin is on here as well and it's off the scale. Other than that, it's actually quite difficult because it's quite an emotive response you're dealing with amongst physicians in terms of their level of comfort around prescribing something new.				Atorvastatin, because it's so large relative to rosuvastatin, that's where the impact of the switching has been felt the most but there have been instances of rosuvastatin low dose being switched as well. It's perhaps a bit more difficult for a prescribing advisor to push a rosuvastatin switch programme because of the clinical data. There's a fairly good argument to say that Atorvastatin 10mg is the best equivalent to simvastatin 40, whereas it's been more difficult to argue that for rosuvastatin			

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		It's just a case of reassurance, to present the safety data in context against the other statins. To try and demonstrate to physicians that look, it's exactly in line with the other available statins. Perhaps we did have a bit of a problem in terms of the way that the product was being used, that's now been addressed and the initiation rates at the start dose are actually very good and actually much better than what you'd get from the SPCs of the other statins							
		I think that the regulators were also a bit more cautious and were keen to issue a letter because of what had happened with cerivastatin. Because it was rhabdomyolysis which, they had fatal cases of rhabdomyolysis; I think there were 50 odd cases of fatal rhabdomyolysis so the regulators are now in a more cautious place and keen to act quickly. So once you kind of send a letter, a prescribing reminder that's citing a risk of rhabdomyolysis in a market where there's already been a product withdrawal because of rhabdomylisis then that spooks physicians and that's responsible for some of that uptake. This is also kind of the time frame when there was a real gearing up behind simvastatin as well. So put those two things together and that's the kind of flattening of, the less steep trajectory of that line around kind of late 2004 onwards.							

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Gen1		We did a lot of work in terms of understanding what it was that was the misconceptions, what needed to be communicated more clearly, and also what materials we could provide that may support the customer. So what could support the GP or the specialist to make it easier for them to work with the patient, so if they had some uncertainty around what they needed to do, they would have some support items that were purely educational and they'd be able to sort of say, okay, if they gave the drug, or any drug, to the patient 'here's the leaflet to say this is what you should do and how you should take it'				Until evidence came of mortality benefits which came with the 4S study, there was very little treatment even though we were saying, you know 'you need to treat, you need to treat', but nobody believed until you got the evidence. You eventually got the evidence and the treatment paradigm changed overnight, from flat to whoosh like this, and then just powered on to be the biggest market in the world. Well, you know, there's still massive under-treatment of that, even though it's the biggest selling drug.			
Gen2					For registration you have to have two placebo controlled studies for licence. So that's why people produce placebo, because we have to, the regulations to actually get the drug licensed. What the regulators want versus what the market access side want, are completely different things.	It's sometimes quite difficult to work out what your comparators need to be. In some therapy areas, standard care in other countries is now not the same standard of care in the UK, so that in itself is proving quite problematic. What we're starting to see in the UK is divergence of clinical practice from the rest of Europe so from some therapy areas potentially oncology, the drugs that are now standard in the rest of Europe are not standard in the UK so…it becomes incredibly expensive, I mean the clinical trials are tremendously expensive to run and it can be quite difficult if you were having to run them for individual countries, and they cost £30 million, £40 million a trial, and you're never going to make the money back.			
					One of our key things is who do we need to talk to? Where is the funding? Because sometimes its not that obvious where the funding is, because actually unless we talk to people who hold the funds, then we have no chance at all				

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					of having a reasonable conversation about prescribing or being able to know who needs taking into account when you're generating your evidence.				

Framework 8: Final Framework for the Evidence Theme Incorporating Data from All Case Studies (post-analysis)

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	Marketing Evidence (REVISED THEME TITLE)	Impact of clinical evidence							
		Impact of evidence	Trial design			Evidence translation: Relevance/ limitation of trial outcomes (RENAMED)		Temporal impact of evidence	Journal quality/ publication control
			Trials design	Functional versatility of evidence (NEW SUB-CATEGORY)	Novel trial perspective (NEW SUB-CATEGORY)	Head to head comparisons	Surrogate markers vs clinically relevant outcomes (MODIFIED SUBTHEME)		
BP1				There is genuinely a concern that etidronate as a first generation bisphosphonate, that if you give it in too a higher dose then it causes osteomalacia which is basically malformed bone, so that the bone that it's making is not of a sufficient quality. And we know that, it came out from the sciences, and the solution from a scientific point of view was to give it in cyclical regiment, so that's why it became Didronel PMO [etidronate] and had a cyclical regimen of 14 days of Didronel followed by the calcium, vitamin D…that's all done to stop osteomalacia occurring because in that dosing cycle it doesn't happen. The US have higher concerns about that than the European regulators, so, it's not unusual that different regulators have different concerns. You could, as a company, submit new data to shift the opinion of the regulators, but you reach a point relatively quickly when you get regulatory delay, that because of the intellectual property rights that you have on the product it becomes unviable to bring it to market within the time space you have back to actually recoup your additional costs and your base costs. It went on and got a licence in Europe, but it never managed to get a licence in the US. (MOVED FROM SAFETY/REGULATION THEME BACK INTO EVIDENCE WITH THIS NEW SUBCATEGORY)					
BP2			I think what disappointed us, and I think there's two things, one is fortuitous, I think that the bisphosphonates are a very good class of drugs, so I will be honest with you I think they all work, and they're all substantially above what you're basic calcium vitamin D does, so that's the great news for the class yes? The bad news, because they all work, that when you try and plan in 1993 what you're expecting breakthrough to do, which was that we were	And at that point we needed to shoot above where MSD were in terms of their studies so they had done BMD, they had done vertebral fracture, they hadn't really had hip fracture as a primary end point, but they key element was that we had a hip fracture drug at the primary end point where hip fracture was prospectively planned, and then obviously the study was sizably geared to show that, so you're looking at 10,000 patient plus. But we had 330 investigators, 16,000 patients, 18 countries.	Large scale trials do carry weight but I think the problem is that as soon as they carry some weight they also become the next benchmark.	Our cost of entry is becoming increasingly higher and the next one is that there's not going to be a head-to-head trial on hip fracture between any drugs, because when they all work as well as all of these do you're talking about 50,000 patients, five years before you even stand a chance of seeing any difference, and when you see the difference it's unlikely to be clinically that significantly and meaningful to actually			We were very heavily focussed on securing a very credible publication for our hip fracture trial published in NEJM and NEJM is still regarded as the highest impact factor publication, out of all the publications you can have. The downside is that they're very fastidious about how things work, so the first thing is that you can't do the gradual release it has to be brand new to the world, otherwise it never gets into NEJM, and so it puts a lot of

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			planning to show a significant reduction in hip fracture that no one else would have, we actually got trumped by Fosamax (alendronate) because they showed fortuitously because it was never powered to show it, they showed fortuitously that they did reduce significantly reduce hip fracture in their trials, because they had a good drug, and we had a good drug, you know, so the reality is that had they not shown hip fracture, had they only ever shown vertebral fracture, which is what we were predicting at the time, then ours, because it was powered to show hip fracture, should have been able to do the bit where it became the market leader.			knock one out of the market and favour the other.			blocks on what you can do, because from a marketing point of view, we want to be able to build up to it, but they won't do that, and that's why they're so prestigious.
									The other element is that they shape the publication, so actually it's from a technical point of view it's not the best written publication, it doesn't do justice to the dataset that supports the publication, but we again don't have a lot of say in that because it's NEJM and they have a lot of say in what they want and how they want it written
									I think we do make mistakes and I think we probably, as a company, we have often maybe jumped a step in terms of dose ranging so we have an issue in the sense that it's not a problem from a clinical point of view, but I have an issue from a trial point of view that our 2.5 milligram arm disappeared out of the trials and so that's not good because you have to explain it, so we should maybe have dealt with that in a different way. We also had an issue that we wanted to do too much in one trial, so what we chose to do was we chose to have an over 80s group, and again a potentially big market, a

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									potentially big unmet need, but we complicated it. So instead of one nice clean crisp message we ended up with sort of 'well I have to explain a few things about my trial before I can now give you my clean crisp message' so it's not so clean and it's not so crisp. And so I think that's maybe our inexperience in…I think a more experienced pharmaceutical company that is doing this day in and day out and has a cookie cutter of 'this is how we launch a drug' they have the experience, you know, and that is a genuine challenge for a company of our size, which is actually how do we keep up the capability in tasks that are infrequent but important?
BP3	Clearly the trial designs that are done for regulatory purposes need to also meet the needs of being able to communicate the benefits of the medicine to the wider community, because you won't have typically in market studies for some years until after the medicine is launched. So you need to have robust data which is going to be able to present to people, regulators, to payers, to physicians, to everybody that actually gives a compelling story of why we would use the drug. So marketing gets involved before launch is what I'm saying	Trials get you your position in guidelines. And there are different quality of trials of course. You've got your Phase III regulatory filing, which is against placebo, which just shows the thing works. If it's a highly competitive field, people like to have head-to-head studies versus the leading comparators, or use drugs in the field at the right dose so that they can make a valid judgement call saying 'well this one is better than that one' and they can say they're efficaciously the same but one does this with less side affects and therefore is better pay off for the doctor and the patient. And that will then influence the positioning in the guidelines, so you have to have the trials, the best form of course, which really prove outcomes (MOVED FROM TRIAL DESIGN)		regulators around the world all have different, slightly different nuances on what data they want to see, which makes it expensive to bring a medicine to market, because you can't necessarily use the same file around the world, and that is a frustration through the industry, and it slows access to medicine down. And it costs us money. So that's a frustration, but that's the world that we live in (MOVED FROM SAFETY/REGULATION THEME BACK INTO EVIDENCE WITH THIS NEW SUBCATEGORY)	trials and guidance do influence , well, trials do. Mega trials are very important in terms of getting the opinion leaders to buy into the science quite frankly.		it's very difficult to do head-to-head trials to prove clinical difference versus an existing field in a drug which you need to do a three to six year study, in a massive population to be powered statistically to prove anything. It's extremely difficult. So you've got to find other markers. In this case that's typically done through bone mineral density which you can actually measure at a relatively short phase and see change, and that would be typically what people will do to try and get an edge over each other	Fracture discharge, as we would describe it became….that was well-published in all leading journals and has become one of the great case studies in this field. And they're very evidence-based and it was all very evidence-based and so that's why they were preferring to use Alendronate maybe than the competition because they've got the fracture intervention trial plus other evidence, plus the 70 milligram formulation.	
				So, you know in the Alendronate case for					

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				us it was very important that we had the fracture intervention trial which was published in about 1996. For a big outcomes trial, three year outcomes trial on fracture which really no fracture data of that scale existed in this field before that trial, and to bring that to market less than a year after the launch of the drug was a hugely important thing to do in getting the diffusion of the drug in a very under treated disease. So, that was a good example of a huge …of this designing the trials correctly for Phase III to be extended to produce the outcomes which gives you every argument.					
				it's also very important to design those studies in a way where you capture data for socio-economic, health economic cases that you can build for to understand the pricing of the medicine. You know, that's not just done by whim, it's done by a form of science. I mean it is an art, and it's also a measure of the competitiveness of that field, but if you're first in the market with a brand new medicine, with a brand new class, how do you price it? You know, you've got to find some means of demonstrating value of the brand and the product to the people who are going to pay for it					
PDE1					The thing that Pfizer did very well I think was, we studied Viagra in everyone. This is the point, this is where the evidence I think became increasingly important because we could say, here's our data on diabetes, here's our data in spinal cord injury and you know, psychological cases, and no competitor during that period was ever going to have anything like that. It showed its effectiveness, but it also forces people to compete across loads of different areas, which is very difficult for them to do and raises the cost of entry so we were always going to have a very high	If you actually look at the wealth of information out there I think Viagra's got something like, I don't know, five, ten times more clinical papers than we have on the sheer numbers of it. But if you look at our numbers of head-to-head studies versus them and if you looked at, say, preference, although each of the drugs have got some studies or abstracts which show a preference for one of the other, there's probably more out there, both sponsored and independent, which would show a preference for tadalafil. But that hasn't swayed things		

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					market share, you know, very early on.				
PDE2			A [KOL] turned around and said 'Look, if you're going to do a study head-to-head, this is how you would do it for the PDE5s and it should be open label, crossover randomised', you know, on the right doses, comparing relative doses, given the package instructions and not going beyond that. He designed the trial and we went and did it.			There are a whole load of different preference studies which were being used at the time but they all had methodological problems. So different doses comparing each other and different instructions and all sorts of weird things going on			
						Ever since this point, end of '05, '06, you've then got a whole load of clinical papers that... ever since launch, physicians have been screaming out for comparative evidence. Show us head-to-head. Tell you what, go and look at the evidence base for head-to-heads now. All the companies have done them to one degree or another. And there's only pretty much one company who are absolutely driving head-to-head studies and that's us. And I think that speaks volumes for where we stand on the medication. You don't have those at launch you have pretty much registration studies which are...we work and here's the reason to care, unique selling point of it (MOVED FROM TRIAL DESIGN INTO NEW HEAD TO HEAD COMPARISON SUBCATEGORY)			
PDE3	I think possibly one of the reasons why we stay down this end of the market is because we don't do as many studies or trials as the other two products, and we all know; it's almost like a self fulfilling thing, we don't do as many because we're not making as much								understand you know, the need for peer-review and everything, but then maybe you leave the review of the data until there's a bit more published data on the other two treatments or you know, I don't know, but it was kind of like, yeah, as much as we tried to discuss it with them, because they give you the opportunity to discuss; it kept coming back to

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	money, but you know we might make more money if we do more studies, so I think it definitely; from a marketing point of view, it really helps, because you can keep saying the same things but bring new data to the package which then makes it sound new and interesting, whereas if you've got old data that you're just sort of re-hashing all the time, you struggle to make something sound new or interesting, so I think clinical data does have a significant affect.(MOVED FROM MARKETING SUBTHEME INTO THIS BROADER CATEGORY)								the same thing, that's a poster, that's an abstract, it's not peer-reviewed. Essentially they have to be peer-reviewed to make the meeting, but my understanding is that it's not as critical a review process as maybe a preliminary published paper would go through.
	No we kind of had our global colleagues trying to make you know, a big new study and we've got to do a whole load of PR about this, I think the initial regulatory submissions, the studies that we used there, they're the best quality evidence, and I think they still really work for us.								
AA1	The data possibly helped to drive some of it, but I think more of that increase you can see was actually driven by the use in elderly patients, I mean the Csernansky data was very very good data. You probably could have argued that we didn't do enough with it, you know, in terms of promoting the data, because it's very good data. Just limits in terms of marketing spend, you know, Jansen-Cilag	efficacy, that has to be proven with all drugs, so you have to have clinical data that shows you're efficacious, and clinical data that shows that you're well tolerated as well, but efficacy is probably the one driver across all brands (MOVED FROM TRIAL DESIGN TO IMPACT OF EVIDENCE)							it's not really until you get a full blown publication, if you can in a prestigious journal, that would have the most impact, so, you know, if it was in like the Lancet, the BMJ, the data published in those journals would have more impact than data published in a lesser renowned journal.

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	would generally have a much lower marketing budget than Lilly for example.								
	we had good effective marketing, that was key in driving the success of the brand. We had to have the clinical data as well, but the marketing activity I think really had more of an emphasis on driving the brand's success. Now I think you can - you still have to invest in the marketing, but unless you have the clinical data to back up the marketing, it's far less effective	The most powerful data is sort of, you know, the early clinical data, so the phase IIIb, particularly if you have randomised head to head, you know, double blinded type data, I mean that's regarded as the most powerful data. The systematic reviews are generally regarded as not quite as robust sometimes, although they can be very useful in terms of gathering lots of different opinions together and forming and overall consensus (MOVED FROM TRIAL DESIGN TO IMPACT OF EVIDENCE)							
	I think what we've seen is an increasing importance of things like the robustness of your clinical data, and therefore the strength of the clinical trial programme that you've run, so do you have for example head to head comparators with products already on the market that shows that you have the benefit in clinical effect or health economic value, and that has really increased in importance (MOVED FROM TRIAL DESIGN)								
AA2 + 3		quality of the data is absolutely paramount to us for a successful product launch. we have to do placebo for regulatory reasons. Physicians want head to head, how do you compare with other products on the marketplace? If you're			we only actually used two or three studies at the time of that launch. The most pivotal of which was the Tollenson data. I recall at the time it was the biggest ever study undertaken on a psychiatric population	At that time we had no head to head data versus risperidone. The differentiation was against the typical antipsychotics, notably haloperidol which did present some problems in the UK because haloperidol, although the standard of care in the US, is less commonly used in the UK and indeed		People go to conferences to get the latest stuff so they definitely take note of what's presented at meetings and you can't beat peer review journal publications.	It will depend on the quality of the study and where it's published as to whether we would react to it . You've always got to look….you know we have to present lots of evidence for our products and so we tend to….if we get an individual study that comes out and look at what is the body of evidence that either backs that

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		lucky enough not to be, you know you're first in class then it's slightly different but quality data is critical (MOVED FROM TRIAL DESIGN TO IMPACT OF EVIDENCE)				across much of Europe. So haloperidol was really seen as a proxy for typical antipsychotics and people were left to draw their own conclusions about what that meant against their own personal standard of care. Be that another typical, such as chlorpromazine or against risperidone. But I remember one of the great needs and the great pleas from our sales forces at the time was we need head to head data versus risperidone which we simply didn't have.			study up or disagrees with that study, if it's a one off and there's loads disagreeing with it I probably wouldn't bother with it. If it's one of a series and I think longer term it's going to hurt the brand if we don't respond to it, then we'll go proactive and respond to it.
								There was such a pent up demand for this drug. And I remember being at some of the congresses where the Phase III data were presented on Zyprexa prior to its launch. And it was standing room only in some of the auditoria where the data were presented. People really were excited about this. That it did represent a breakthrough	
AA4		Our objective is to become the number one oral atypical, and actually, if all these drugs work exactly the same, you know, so in terms of their level of effect is the same, and that's what NICE says, why is it that the drug that actually causes patients the least problem is only 3rd not 1st in the market?...it should be a lot higher up than it is (MOVED FROM HEALTH SERVICE AND POLICY ENVIRONMENT TO EVIDENCE).					I think you would struggle to identify a really ground breaking study that kind of meant people used atypicals instead of typicals, one, because of the nature of the illness and the nature of how clinical trials are done. So when you measure, do a trial for a statin and you are measuring cholesterol, you have your primary outcome measures for that trial will be things that doctors that are prescribing them, totally understand. If I talk about a PANSS scale or a Weinmeres scale or any of those scales they are kind of, not artificial but they are a thing that is done in order to get clinical trial results and not just by the industry but that's how you measure the effectiveness of the		

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			Trials design	Functional versatility of evidence (NEW SUB-CATEGORY)	Novel trial perspective (NEW SUB-CATEGORY)	Head to head comparisons	Surrogate markers vs clinically relevant outcomes (MODIFIED SUBTHEME)		
							drugs. Your jobbing day to day psychiatrist may not really understand exactly what a reduction in PAN score means to a patient unless they are involved in clinical trial work.		
Statin1					What was going to change the cholesterol lowering market was big trials. If ever there was an area that is characterised by there having been an impact of big randomised controlled trials, it's this area, so I think it was 1994 that the first sort of big landmark study came out, the 4S study, and there for the first time was a demonstrated impact on total mortality, not cardiovascular mortality, but total mortality in a population of middle aged men with existing heart disease and I think that was the turning point at which erm people started to really kind of, sit up and take notice. I mean there had been pretty good evidence beforehand, but not in such a simple, elegantly designed, big trial as happened then and I think you really start to see from the back end of '94 that things really start to take off	MSD staked their place as market leader for many years really with the 4S trial; they had what was probably of the available statins, the most effective lipid lowerer and they had the evidence to say this drug saves lives and I think , that's reflected in their usage relative to the others. The other drugs were either later or less convincing with their trials, so there was actually very good evidence for Pravastatin, but Pravastatin probably published more landmark trials, through the nineties than Merck did behind Simvastatin, but the drug was less effective at lowering cholesterol and it was the most effective drug in the market place that benefitted.	Then along came Lipitor, atorvastatin; more effective still and by the time we launched, in the late nineties…the kind of medical world had made its' mine up, that cholesterol lowering was a good thing, that there was probably a class effect at work here, so probably all of the statins worked, and so which one were you going to use, well you were going to use the ones which lowered the cholesterol the most, and that's what led to the early uptake of Lipitor. As our clinical trial programme progressed, we began to publish trials that indeed demonstrated that Lipitor shared the benefits and in fact may have a greater effect on mortality than Simvastatin did, and that's when you saw the real kind of take off , through the early 2000's when there was the confirmation that that additional cholesterol lowering did translate to real benefit and of course , the period of sort of 2001 through to 2004 was enormous for us. (MOVED FROM COMMUNICATION OF RELATIVE ADVANTAGE THEME TO EVIDENCE)	We've almost got to the point of there being just sheer overkill on the amount of data, I mean how much more evidence do you need that lowering cholesterol saves lives, and there's not much, not many questions left to ask now really.	
Statin2		I think if we hadn't had these Dear Doctor letters this gap here shows you the evidence is not that important. It is now because this happened and people want to see evidence, so if you start it again here, you'd say yes some of the trials have been important but during that first dynamic phase evidence wasn't important to us. Everyone had					You have to really ask the question do you believe that it's an LDL story or not? So from 4S onwards every single statin trial that's come out has shown that lowering LDL cholesterol is beneficial. So are you saying that one statin is a miracle drug, or are you saying it's really largely its ability to lower LDL cholesterol? Now if you look at all them together and say okay, then you have the ileal bypass trial, POSCH, which saved lives without any statins, by lowering LDL cholesterol. You have the	There's not much more evidence you can collect really because most of it's been done in terms of placebo controlled trials, most of it's been done now. It's mostly unethical to do the trials anymore. So we're stuck. So doing more and more trials is probably not the answer, pharmacoeconomics is	

Interview	Evidence Theme/Subthemes								
	Marketing Evidence (REVISED THEME TITLE)	Impact of clinical evidence							
		Impact of evidence	Trial design			Evidence translation: Relevance/ limitation of trial outcomes (RENAMED)		Temporal impact of evidence	Journal quality/ publication control
			Trials design	Functional versatility of evidence (NEW SUB-CATEGORY)	Novel trial perspective (NEW SUB-CATEGORY)	Head to head comparisons	Surrogate markers vs clinically relevant outcomes (MODIFIED SUBTHEME)		
		bought into the fact that lowering LDL is good for you (MOVED FROM ADVERSE EVENTS TO NEW SUBTHEME)					Cholestepol trials which saved lives by lowering cholesterol. And so if you draw a line from the top to the bottom, you can plot all these trials on a line that basically shows you the lower the LDL cholesterol the better your outcome is. So that's your surrogate market argument. We can lower LDL cholesterol, we can prove it does things to atherosclerosis.	the answer I think. Make sure that your product is pharmacoeconomically positioned to take advantage of the health system as it is now	
Statin3	It's a very highly regulated industry in terms of what you can and what you can't present to clinicians. We can convey the results of clinical studies and you can say that that's marketing, you can say that that's science. But I think there's a case to say that it's…certainly in the UK it's, it's pretty difficult to over market a drug just because of the level of regulation. It's that relationship between regulation and marketing and some of the sign off procedures that we have to go through internally such that the representatives can actually share the material with a physician are kind of ludicrous but it's there to protect the industry and the clinicians.					I guess the main one, the one that is mostly used within the marketing is the STELLAR trial where the endpoints are cholesterol markers and mainly because it's comparative data across the statins, it's head to head data. A lot of the trials are not head to head but it's possible to do that on cholesterol… when we get our outcomes data then the focus would switch a bit, it's true what we've been telling you, a reduction in cholesterol and it has an event and outcomes benefit.	Some physicians will be completely closed off in terms of if there's no clinical outcomes data I'm not touching it, and that's fair enough. Others are willing to accept that there's a relationship demonstrated in other studies in the past between reducing cholesterol and reducing CV events. We have to be very careful in our marketing because we're only licensed for cholesterol. We cannot imply in out marketing that Crestor reduces CV events because that data has not been demonstrated. We can show evidence from other studies, but we have to clearly associate them with the drugs that were in those studies and say Crestor lowers cholesterol then it's up to them to make the link if they want to (MOVED FROM COMMUNICATION OF RELATIVE ADVANTAGE THEME TO EVIDENCE)	There was awareness of the clinical data before launch and that it looked fairly strong. Other things that were in place like the QOF which physicians were starting to get wind of which directly incentivises them to go and find patients who were eligible for statin therapy and to treat them to a certain level, those two things together, that's some of the reason behind that.	
							Atorvastatin, because it's so large relative to rosuvastatin, that's where the impact of the switching has been felt the most but there have been instances of rosuvastatin low dose being switched as well. It's perhaps a bit more difficult for a prescribing advisor to push a rosuvastatin switch programme because of the clinical data. There's a fairly good argument to say that Atorvastatin 10mg is the best equivalent to simvastatin 40, whereas it's been more difficult to argue that for rosuvastatin.		
Gen1							Until evidence came of mortality benefits which came with the 4S		

Interview	Evidence Theme/Subthemes								
	Marketing Evidence (REVISED THEME TITLE)	Impact of clinical evidence							
		Impact of evidence	Trial design			Evidence translation: Relevance/ limitation of trial outcomes (RENAMED)		Temporal impact of evidence	Journal quality/ publication control
			Trials design	Functional versatility of evidence (NEW SUB-CATEGORY)	Novel trial perspective (NEW SUB-CATEGORY)	Head to head comparisons	Surrogate markers vs clinically relevant outcomes (MODIFIED SUBTHEME)		
							study, there was very little treatment even though we were saying, you know 'you need to treat, you need to treat', but nobody believed until you got the evidence. You eventually got the evidence and the treatment paradigm changed overnight, from flat to whoosh like this, and then just powered on to be the biggest market in the world. Well, you know, there's still massive under-treatment of that, even though it's the biggest selling drug.		
Gen2				For registration you have to have two placebo controlled studies for licence. So that's why people produce placebo, because we have to, the regulations to actually get the drug licensed. What the regulators want versus what the market access side want, are completely different things.		It's sometimes quite difficult to work out what your comparators need to be. In some therapy areas, standard care in other countries is now not the same standard of care in the UK, so that in itself is proving quite problematic. What we're starting to see in the UK is divergence of clinical practice from the rest of Europe so from some therapy areas potentially oncology, the drugs that are now standard in the rest of Europe are not standard in the UK so…it becomes incredibly expensive, I mean the clinical trials are tremendously expensive to run and it can be quite difficult if you were having to run them for individual countries, and they cost £30 million, £40 million a trial, and you're never going to make the money back.			
				One of our key things is who do we need to talk to? Where is the funding? Because sometimes its not that obvious where the funding is, because actually unless we talk to people who hold the funds, then we have no chance at all of having a reasonable conversation about prescribing or being able to know who needs taking into account when you're generating your evidence.					

Appendix 11: Iterative Development of the Analytical Thematic Framework Coding Categories for All Themes

Framework 1: AAs - Post-coding

1. **Clinical Need**

2. **Clinical Experience**

3. **Evidence**
   - 3.1. Legitimacy (authority)
   - 3.2. Quality
   - 3.3. Primary studies
     - 3.3.1. Timing
     - 3.3.2. Rejection/Acceptance
     - 3.3.3. Relevance of clinical endpoints
   - 3.4. Warnings/safety concerns

4. **Disease area characteristics**
   - 4.1. Clinical priorities
   - 4.2. Patient perspective

5. **Drug characteristics**
   - 5.1. Real benefits
   - 5.2. Perceived benefits
   - 5.3. Ease of use
   - 5.4. Differentiation
   - 5.5. New formulations

6. **Market expansion**
   - 6.1. Education
   - 6.2. Identifying leakage points (where patients are lost)
   - 6.3. New indications
   - 6.4. Heritage
   - 6.5. Growth Limiters

7. **Market preparedness/access**
   - 7.1. Market research
   - 7.2. Competitors

8. **Communication channels**
   - 8.1. Advertising
   - 8.2. Clarity of message
   - 8.3. Message reinforcement (reps)
   - 8.4. Endorsement

9. **Market leadership**
   - 9.1. Company perception
   - 9.2. Responsibilities

10. **Policy and Government**
    - 10.1. Priority areas
    - 10.2. Mandatory guidance vs guidelines
    - 10.3. Timing

Framework 2: AAs - Post-analysis

1. Clinical Need
- 1.1. Degree of anticipation
- 1.2. Severity of condition
- 1.3. Ease of use

2. **Relative Advantage – innovation** – may become wider heading of innate characteristic.

3. Clinician Experience

4. Evidence
- 4.1. Safety
  - 4.1.1. Unlicensed use
  - 4.1.2. Regulatory warning
  - 4.1.3. Adverse effects
- 4.2. Clinical Data
  - 4.2.1. Primary
  - 4.2.2. Secondary
- 4.3. Evidence Translation
  - 4.3.1. Relevance of outcomes
- 4.4. Policy and guidelines
  - 4.4.1. Mandatory nature
  - 4.4.2. Differentiation
  - 4.4.3. Timing

5. Disease Perception
- 5.1. Risk mitigation
- 5.2. Infrastructure – Institutional barriers

6. Innate characteristics
- 6.1. Real vs perceived benefits
- 6.2. Idiosyncratic responses

7. Market Preparedness – may include education in here?
- 7.1. Market entry position
- 7.2. Market research – linked clinical need
- 7.3. Supply logistics

8. Communication
- 8.1. Clarity of message
- 8.2. Managing expectations
- 8.3. Message Reinforcement
  - 8.3.1. Priority and resource allocation/Co. size
  - 8.3.2. Endorsement
  - 8.3.3. Advertising

9. Market Leadership
- 9.1. Market expansion
- 9.2. Education
- 9.3. Research – new formulation/indications

10. Maintaining Perception of Brand/Co. credibility
- 10.1. Rescue strategies
  - 10.1.1. Redefining meaning/ change messaging
  - 10.1.2. Switching focus
  - 10.1.3. Proactive responses
- 10.2. Competitor - objection handling
- 10.3. Heritage

11. Patient Input

Framework 3: BPs - Post-coding

1. Clinical need/demand (Clinician/patient experience)
- 1.1. Interdependence of diffusion factors
- 1.2. Patient experience, expectations and compliance

2. Clinical Experience

3. Evidence
- 3.1. Safety
  - 3.1.1. Unlicensed use
  - 3.1.2. Regulatory Issues
  - 3.1.3. Adverse effects
- 3.2. Clinical effectiveness (Primary level data)
  - 3.2.1. Trial design
  - 3.2.2. Journal quality/Publication control
- 3.3. Evidence translation
  - 3.3.1. Trial outcomes: planned vs serendipitous
  - 3.3.2. Tailored to adopter category (Clinical relevance of outcomes)

4. Health Service Environment
- 4.1.1. Policy and Guidelines (Secondary level data)
  - 4.1.1.1. Political priority
  - 4.1.1.2. Conversion of policy/guidelines stance to industry aim
  - 4.1.1.3. Clinical setting of disease management – specialist/non-specialist.
  - 4.1.1.4. Mandatory nature
  - 4.1.1.5. Strength of message/ competitor differentiation
  - 4.1.1.6. Timing
- 4.1.2. UK Constraints
  - 4.1.2.1. Clinician conservatism
  - 4.1.2.2. Infrastructure/institutional barriers

5. Disease Perception
- 5.1. Risk mitigation (inexperience leading to lack of confidence)
- 5.2. Reduced health service priority
- 5.3. Clinician indifference/dismissiveness
- 5.4. Alteration of perception through disease awareness

6. Innovation's innate characteristics
- 6.1. Relative advantage (was initially separate category)
- 6.2. Real vs perceived benefits
- 6.3. Idiosyncratic responses

7. Market Preparedness
- 7.1. Market entry position
- 7.2. Market research
  - 7.2.1. Industry dependence
- 7.3. Access management (non-prescribers)
- 7.4. Supply logistics
- 7.5. Managing expectations (should go into communication?)

8. Communication
- 8.1. Clarity of message
- 8.2. Message reinforcement
  - 8.2.1. Priority/ resource allocation linked to Co size
  - 8.2.2. Representative (detailing) – heterophily – was under broader heading of endorsement that also incorporated KOLs which been moved to separate category.
  - 8.2.3. Advertising
    - 8.2.3.1. Targeted cascade approach
  - 8.2.4. Dissemination

9. KOLs
- 9.1. Collaborative involvement with industry
  - 9.1.1. Loyalty to one company causing institutional inertia
- 9.2. Peer credibility/acceptance
  - 9.2.1. Hierarchical
  - 9.2.2. Esteem based on access to exclusive information
- 9.3. Collegiate agreement
  - 9.3.1. Advisory/ Educational motivation

10. Market Leadership

- 10.1. Entitlement – company resolve
- 10.2. Market expansion responsibility
  - 10.2.1. Education
  - 10.2.2. Overcoming Infrastructure barriers (Funding of NHS services 'corporate philanthropy')
  - 10.2.3. Research new formulations/indications

11. Maintaining perception of brand integrity/ Co. credibility

- 11.1. Rescue strategies
  - 11.1.1. Redefining meaning/change messaging
  - 11.1.2. Switching focus
  - 11.1.3. Proactive responses
    - 11.1.3.1. Implementing/supporting services under-funded by NHS
- 11.2. Competitor/objection handling

12. Corporate Heritage

- 12.1. Inexperience
- 12.2. Mergers and acquisitions
- 12.3. Corporate identity

13. Lifecycle strategies

- 13.1 Uptake acceleration

Framework 4: BPs - Post-analysis

1. Clinical need/demand (Clinician/patient)
- 1.1. Technology void
- 1.2. Discontent
- 1.3. Innovator pursuit -'be first mentality'

2. Clinician Experience

3. Evidence
- 3.1. Safety
  - 3.1.1. Unlicensed use (formerly off-label)
  - 3.1.2. Regulatory issues
    - 3.1.2.1. Variation in regulatory standards
    - 3.1.2.2. Adverse effects (official warnings)
- 3.2. Clinical effectiveness (primary data)
  - 3.2.1. Trial design
  - 3.2.2. Temporal impact of evidence
  - 3.2.3. Relevance/limitation of trial outcomes
  - 3.2.4. Journal quality/Publication control

4. Health Service [policy] Environment
- 4.1. Policy and Guidelines (Secondary data)
  - 4.1.1. Political priority
  - 4.1.2. Strength of message/Differentiation/Conversion to industry aim
  - 4.1.3. Hierarchy of perceived importance - mandatory nature
  - 4.1.4. Timing
  - 4.1.5. Clinical setting of disease management – specialist/non-specialist.

5. Clinician/Patient Attitude
- 5.1. Clinician conservatism
- 5.2. Disease Perception (indifference/nonchalance)
- 5.3. Risk mitigation

6. Innate characteristics of the Innovation
- 6.1. Relative advantage
- 6.2. Real vs perceived benefits
- 6.3. Idiosyncratic responses

7. Market Preparedness (or Market Access Preparation/Management?)
- 7.1. Market entry position
  - 7.1.1. Premature curtailment of the market
- 7.2. Market research
  - 7.2.1. Industry dependence
- 7.3. Non-prescriber argument
- 7.4. Supply logistics
- 7.5. Managing expectations

8. Communication
- 8.1. Clarity (Simplicity) of message
  - 8.1.1. Tailoring to adopter characteristics
- 8.2. Message reinforcement
  - 8.2.1. Priority and resource allocation (Partnering, mergers and acquisitions)
  - 8.2.2. Targeting of the message
  - 8.2.3. Representative (detailing) – translation process of trust)
  - 8.2.4. Advertising
  - 8.2.5. Dissemination

9. KOLs
- 9.1. Hierarchical cascade of influence
- 9.2. Early engagement/collaboration
- 9.3. Loyalty causing institutional inertia
- 9.4. Peer credibility and esteem
- 9.5. Collegiate agreement – management consensus

10. Market Leadership
- 10.1. Market expansion

10.1.1. Disease awareness
10.1.2. Education – aid decision making
10.1.3. Subsidy of health services (corporate philanthropy)
10.1.4. Research - new formulations/new indications

11. Image - Maintaining brand perception/ Company integrity

11.1. Rescue strategies
11.1.1. Redefining meaning/change messaging
11.1.2. Switching focus
11.1.3. Proactive responses
11.2. Response to competitors (objection handling)

12. Heritage (corporate identity)

13. Interdependence of diffusion factors

Framework 5: Combined AAs + BPs + PDE5s - Post-coding

1. Clinical need/demand (Clinician/patient)
- 1.1 Technology void
- 1.2. Discontent
- 1.3. Innovator pursuit -'be first mentality'

2. Clinician/Patient Experience
- 2.1. Real life experience
- 2.2. Use of samples
- 2.3. Autonomy – compromising freedom to gain experience

3. Evidence
- 3.1. Safety
  - 3.1.1. Unlicensed use
  - 3.1.2. Regulation
    - 3.1.2.1. Variation in regulatory standards
    - 3.1.2.2. Adverse effects (official warnings)/ contraindications
- 3.2. Clinical effectiveness (primary data)
  - 3.2.1. Trial design
  - 3.2.2. Temporal impact of evidence
  - 3.2.3. Translation: Relevance/limitation of trial outcomes
  - 3.2.4. Journal quality/Publication control
- 3.3 Marketing – market revival with new data

4. Environment
- 4.1. Health Policy environment (central government outputs - white papers/NSFs)
  - 4.1.1. Political priority
  - 4.1.2. Policy constraints – discrimination/ impacts on compliance
  - 4.1.3. Conversion to industry aim
- 4.2. Guidelines (secondary data – produced by non-government bodies: NICE/Royal Colleges)
  - 4.2.1. Hierarchy of perceived importance - mandatory nature
  - 4.2.2. Strength of message/Differentiation
  - 4.2.3. Timing
  - 4.2.4. Conversion to policy aim
- 4.3. Health Care Environment
  - 4.3.1. Clinical setting of disease management (specialist/non-specialist)
  - 4.3.2. Clinical priority

5. Attitude: Clinician/ Patient
- 5.1. Clinician conservatism
- 5.2. Disease Perception (indifference/nonchalance/reticence/embarrassment)
- 5.3. Risk mitigation

6. Market Expansion/development
- 6.1. Disease awareness
  - 6.1.1. Counteract attitudes to disease perception through education/de-stigmatisation (by medicalisation/celebrity endorsement)
  - 6.1.2. Patient group role – credible conduit of information
- 6.2. Market leadership responsibility
  - 6.2.1. Subsidy of health services (corporate philanthropy overcome infrastructure barriers)
  - 6.2.2. Research - new formulations/new indications

7. Innate characteristics of the Innovation
- 7.1. Relative advantage
- 7.2. Real vs perceived benefits
- 7.3. Change of mode of administration on clinical setting
- 7.4. Idiosyncratic responses

8. Market Preparedness (or Market Access Preparation/Management?)
- 8.1. Market entry position
  - 8.1.1. Premature curtailment of the market (early generic competition/ counterfeit challenges)
- 8.2. Market research
  - 8.2.1. Industry dependence
- 8.3. Non-prescriber argument/access barrier

8.4. Supply barriers
    8.4.1. Supply logistics
    8.4.2. Dispensing issues
8.5. Managing expectations

9. Communication
9.1. Clarity (simplicity) of message
    9.1.1. Tailoring to adopter characteristics
9.2. Message reinforcement
    9.2.1. Company priority and resource allocation (Partnering, mergers and acquisitions)
    9.2.2. Targeting of the message
    9.2.3. Representative (detailing) – translation process of trust to aid decision making/correct usage of product.
    9.2.4. Dissemination
        9.2.4.1. Controlled – advertising
        9.2.4.2. Uncontrolled – media

10. KOLs
10.1. Hierarchical cascade of influence
10.2. Early engagement/collaboration/interest/enthusiasm
10.3. Loyalty based institutional inertia
10.4. Peer credibility and esteem
10.5. Collegiate agreement – management consensus

11. Image - Maintaining brand perception/ Company integrity
11.1. Brand identity/recognition
11.2. Rescue strategies – response to adverse market conditions
    11.2.1. Redefining meaning/change messaging
    11.2.2. Switching focus
    11.2.3. Proactive responses
11.3. Response to competitors (objection handling)

12. Cultural/scientific heritage (corporate identity)

13. Circumstantial Events

14. Interdependence of diffusion factors

Framework 6: AAs + BPs + PDE5s - Post-analysis

1. Clinical need
- 1.1. Discontent with current therapies
- 1.2. Desire for something new in a stagnating field
- 1.3. Need to alleviate distress
- 1.4. Patients' need to restore normality
- 1.5. Need to satisfy innovator pursuit

2. Clinician/Patient Experience
- 2.1. Subjective evaluation based on personal clinical experience
- 2.2. Clinician-patient interaction
- 2.3. Distorted experience
- 2.4. Patient experience - customer feedback

3. Evidence
- 3.1. Safety /Regulation
  - 3.1.1. Warnings
    - 3.1.1.1. Unlicensed use
    - 3.1.1.2. Adverse effects/contraindications
  - 3.1.2. Variation in regulatory standards
- 3.2. Evidence as marketing
  - 3.2.1. Trial design
  - 3.2.2. Evidence translation: Relevance/limitation of trial outcomes
    - 3.2.2.1. Head to head comparisons
    - 3.2.2.2. Surrogate markers
  - 3.2.3. Temporal impact of evidence
  - 3.2.4. Journal quality/Publication control

4. Health Service/policy Environments
- 4.1. Health Policy Environment
  - 4.1.1. Political priority
    - 4.1.1.1. Restrictive policy
- 4.2. Independent guidance/guidelines
  - 4.2.1. Differentiation
  - 4.2.2. Perceived importance/ Strength of message
  - 4.2.3. Timeliness
- 4.3. Health Care Environment
  - 4.3.1. Clinical priority
  - 4.3.2. Clinical setting of disease management (specialist/non-specialist)

5. Attitude: Clinician/ Patient
- 5.1. Clinician conservatism
- 5.2. Disease Perception
- 5.3. Risk mitigation

6. Communication of relative advantage
- 6.1. Differentiation
  - 6.1.1. Real versus perceived benefits
  - 6.1.2. Brand identity/perception
  - 6.1.3. Market entry position
- 6.2. Message clarity/simplicity
- 6.3. Tailoring to adopter characteristics
- 6.4. Product awareness (advertising) – targeting the message
  - 6.4.1. Managing expectations
- 6.5. Message reinforcement (representatives)
- 6.6. Competitor objection handling

7. Market development
- 7.1. Market research
- 7.2. Disease awareness
  - 7.2.1. Patient group role
  - 7.2.2. Public figure/celebrity endorsement
  - 7.2.3. Media role
- 7.3. Market leadership responsibility
  - 7.3.1. Subsidy of health services (corporate philanthropy)
- 7.4. Research - new formulations/new indications
- 7.5. Dispensing/supply issues

8. KOLs
8.1. Early engagement/collaboration
8.2. Hierarchical cascade of influence/peer credibility
8.3. Advancing the field through collegiate agreement

9. Cultural heritage/Company perception
9.1. Cultural mindset influence on company perception
9.2. Determining company priorities

10. Pricing
10.1. Price setting
10.2. Price perception

Framework 7: (AAs + BPs + PDE5s) + statins + general – Post-coding

The framework categories did not change from the previous version as a result of coding the statins and general interview data.

Framework 8: Final Thematic Framework: All cases - Post-analysis

1. CLINICAL NEED
- 1.1. Discontent with current therapies
- 1.2. Innovation inertia: Desire for something new in a stagnating field
- 1.3. Vocational need to alleviate distress
- 1.4. Disparity between clinician and patient–driven needs
- 1.5. Need to satisfy innovator pursuit
- 1.6. Industry response to unmet clinical need

2. CLINICIAN/PATIENT EXPERIENCE (EFFECTIVENESS)
- 2.1. Subjective evaluation based on personal clinical experience
- 2.2. Clinician-patient interaction
- 2.3. Inappropriate drug use
  - 2.3.1. Distorted experience
  - 2.3.2. Safety warnings/concerns
- 2.4. Patient insight
- 2.5. Industry response to experiential barriers

3. CLINICAL EVIDENCE (EFFICACY)
- 3.1. Marketing evidence
- 3.2. Impact of clinical evidence
  - 3.2.1. Trial design
    - 3.2.1.1. Functional versatility of evidence
    - 3.2.1.2. Novel trial perspective
  - 3.2.2. Evidence translation: Relevance/limitation of trial outcomes
    - 3.2.2.1. Head to head comparisons
    - 3.2.2.2. Surrogate markers versus clinically relevant outcomes
  - 3.2.3. Temporal impact of evidence
  - 3.2.4. Journal quality/Publication control

4. HEALTH SERVICE/POLICY ENVIRONMENTS
- 4.1. Health policy environment
  - 4.1.1. Political priorities
    - 4.1.1.1. Favourable policy environment
    - 4.1.1.2. Adverse policy environment
- 4.2. Independent guidance/guidelines
  - 4.2.1. Differentiation
  - 4.2.2. Perceived importance/ strength of message
  - 4.2.3. Timeliness
- 4.3. Health service environment
  - 4.3.1. Clinical priorities
  - 4.3.2. Clinical setting of disease management (specialist/non-specialist)
- 4.4. Industry response to environmental barriers

5. ATTITUDE: CLINICIAN/ PATIENT
- 5.1. Clinician conservatism
- 5.2. Perception of Industry
- 5.3. Disease perception
- 5.4. Non-specialist risk mitigation
- 5.5. Industry response to attitude barriers

6. COMMUNICATING RELATIVE ADVANTAGE
- 6.1. Differentiating relative advantage
  - 6.1.1 Real versus perceived benefits
  - 6.1.2. Market entry position
  - 6.1.3. Perception of brand identity
- 6.2. Conveying relative advantage
  - 6.2.1. Simplicity/ clarity of message
    - 6.2.1.1. Tailoring the message to adopter needs
    - 6.2.1.2. Targeting the message
  - 6.2.2. Product awareness (advertising)
    - 6.2.2.1. Managing expectations
  - 6.2.3. Product justification (representative detailing)
    - 6.2.3.1. Competitor objection handling

7. MARKET DEVELOPMENT

- 7.1. Market research
- 7.2. Raising disease awareness
  - 7.2.1. Patient group role
  - 7.2.2. Public figure/celebrity endorsement
  - 7.2.3. Media role
- 7.3. Market leadership
  - 7.3.1. Corporate philanthropy: Subsidy of health services
- 7.4. Research: New formulations/new indications
- 7.5. Dispensing/supply issues

8. KEY OPINION LEADERS (KOLS)

- 8.1. Early engagement/collaboration
- 8.2. Hierarchical cascade of influence/peer credibility
- 8.3. Advancing the field through collegiate agreement

9. CULTURAL HERITAGE/COMPANY PERCEPTION

- 9.1. Cultural influence on company perception
- 9.2. Culture determining company priorities

10. PRICING

- 10.1. Price setting
- 10.2. Price perception

Appendix 12: Qualitative study assessment criteria (Mays and Pope, 1995)

Qualitative Study Assessment Criteria

1. Did the researcher make explicit in the account the theoretical framework and methods used at every stage of the research?

2. Was the context clearly described?

3. Was the sampling strategy clearly described and justified?

4. Was the sampling strategy theoretically comprehensive to ensure the generalisability of the conceptual analyses (diverse range of individuals and settings, for example)?

5. How was the fieldwork undertaken? Was it described in detail?

6. Could the evidence (fieldwork notes, interview transcripts, recording, documentary analysis, etc.) be inspected independently by others; if relevant, could the process of transcription be independently inspected?

7. Were the procedures for data analysis clearly described and theoretically justified? Did they relate to the original research question? How were themes and concepts identified from the data?

8. Was the analysis repeated by more than one researcher to ensure reliability?

9. Did the investigator make use of quantitative evidence to test qualitative conclusions where appropriate?

10. Did the investigator give evidence of seeking out observations that might have contradicted or modified the analysis?

11. Was sufficient of the original evidence presented systematically in the written account to satisfy the sceptical reader of the relation between the interpretation and the evidence (for example, were quotations numbered and sources given)?

Appendix 13: Background literature on bisphosphonates for postmenopausal osteoporosis

1. Osteoporosis

Osteoporosis can affect the whole skeleton and most commonly results in fractures to bones in the wrist, spine and hip, causing a substantial burden of disability and chronic pain. Once perceived as a natural consequence of ageing, it is now acknowledged as a major public health concern that is potentially preventable.

Bones are living organs that undergo constant remodelling. Specialist cells called osteoclasts remove old bone, leaving pit like depressions that are filled with new bone deposited by cells called osteoblasts over a period of about 90 days. Cortical bone on the outside is dense and compact, while trabecular bone on the inside has a honeycomb structure to maximise strength whilst minimising weight. In osteoporosis, it is the trabecular bone loss which occurs first with serious implications to bone strength.

While osteoporosis can occur in all populations at all ages, it is most prevalent in postmenopausal women, with symptoms usually developing between ages 51 and 75 years. In addition to age, bone loss may be influenced by several other factors including low body weight, smoking, excess alcohol consumption, physical inactivity, genetic factors poor dietary calcium intake, reduced production and impaired metabolism of vitamin D and declining calcium absorption.

Osteoporosis is sometimes referred to as a silent disease as only around one third of radiographically diagnosed vertebral fractures cause symptoms (Cooper and Melton, 1992). The condition may go unnoticed for several years, until it causes a loss in height or the characteristic marked curvature of the upper back (referred to as a dowager's hump) as the bones in the spinal column become crushed or wedged. Clinically apparent vertebral fractures however, can cause pain, breathing difficulties and gastrointestinal problems, while hip fractures are associated with significant morbidity and mortality.

2. Diagnosis

2.1. Defining Osteoporosis – Bone Mineral Density (BMD)

Despite the production of numerous guidelines, diagnosis of osteoporosis is still controversial, mainly as it is a condition which involves many medical disciplines, all with differing perspectives. Osteoporosis received little attention until the advent of dual-energy X-ray absorptiometry scanning techniques (DEXA) in the late 1980's, which made it possible to accurately measure bone mineral density (BMD). Coupled with the therapeutic possibility of preventing bone loss, osteoporosis was transformed from a fracture syndrome resulting from reduced bone density detected only once a fracture had occurred, to one of reduced bone density even in the absence of fractures.

Table A13.1: WHO definition of osteoporosis

Stages of Osteoporosis	Bone Mineral Density
Osteopaenia	T-score between -1.0 and -2.5.
Osteoporosis	T-score below -2.5
Established osteoporosis	T-score <-2.5, with presence of one or more fragility fractures

BMD T-scores can vary by site and method of measurement so the gold standard for diagnostic purposes is total hip BMD measured by DEXA (Kanis, 2002). Changes to BMD (preferably at the spine) may be used to monitor responses to treatment (Royal College of Physicians (RCP), 1999). About 50% of women with symptomatic vertebral fractures have evidence of osteoporosis (T score <-2.5) on spine bone densiometry, and a further 40% have osteopaenia (T-score -1 to -2.5) (Francis *et al*., 2004).

Population-based BMD screening has never been advocated for the prevention of osteoporotic fractures due to the high cost of DEXA scanning. Instead a selective case-finding approach was recommended, based on other risk factors, such as the presence of previous fracture. There are still relatively few DEXA scanners (bone densitometers) per million of the population in the UK compared with other European countries.

2.2. Issues with BMD

The correlation between low bone mineral density and increased risk of fracture is contentious. Low bone density is an important component of fracture risk, but it cannot be used alone. Other skeletal (bone turnover) and non-skeletal parameters (advanced age and propensity to fall) contribute to fracture risk and need to be considered to predict in absolute terms whether or not an individual will sustain a fracture. For a given BMD T-score of -2.5, a 50 year old woman has a much lower fracture risk than an 80 year old woman (Cheung and Detsky, 2008). It has been proposed that falls are a stronger predictor of fractures than BMD. Falls increase in frequency with advancing age due to an increasing number of cognitive issues and account for at least 95% of hip fractures in the elderly (Wilkins, 1999).

Controversy has surrounded the WHO definition of osteoporosis. Some believe it is inappropriate to use a surrogate marker as by raising it to the status of a diagnostic criterion, it conceptualises a risk factor as a disease (Eastell, 1998). This is however, not an issue restricted just to osteoporosis, but a concern with surrogate markers in general (other examples include cholesterol and heart attacks, or blood pressure and stroke) and ultimately their ability to translate into clinically relevant endpoints.

The fact that the WHO definition set the bone density of young white women as normal, and to judge the bones of older women against this standard was viewed contentiously by some in the medical profession, who have indicated a Z-score measure (BMD is compared with the mean value in normal subjects of the same age and sex) may have been more appropriate (Eastell, 1998; Moynihan *et al*., 2002). Some have implied that the Industry were heavily involved in influencing the WHO definition, through sponsorship of key meetings of the WHO study group, and developing extensive financial ties with leading researchers and patient groups (Moynihan, 2002).

2.3. Fracture reduction

Alternatively osteoporosis can be inferred from the presence of pre-existing osteoporosis-related fractures at the spine or hip detected symptomatically, or defined radiographically.

Previous fracture is an important determinant of predicting future risk:

- In osteoporotic patients without pre-existing fracture, the 3-4 year incidence of new vertebral fracture ranges from 2-4% (Cummings *et al*., 1998; Liberman *et al*., 1995; Ettinger *et al*., 1999), and from 1.1%-5.1% for hip fracture (Cummings *et al*., 1998; McClung *et al*., 2001).
- In contrast, these rates in those with pre-existing fracture increase to 15-29% for new vertebral fractures (Liberman *et al*., 1995; Ettinger *et al*., 1999; Lindsay *et al*., 2001; Klotzbuecher *et al*., 2000; Black *et al*., 1996; Harris *et al*., 1999; Reginster *et al*., 2000), and 2.2-5.7% for new hip fractures (McClung *et al*., 2001; Black *et al*., 1996; Harris *et al*., 1999; Reginster *et al*., 2000).

2.4. Markers of Bone turnover

An increased rate of bone turnover has been suggested by some as a better measure of risk than low BMD, (Wilkin, 1999). The extent to which changes in BMD and biochemical markers account for changes in fracture risk remains an area of much debate (Rosen *et al*., 2005). It has been suggested that the small increases in BMD (5-8%) seen with BPs could not account entirely for the reductions in fracture risk of the order of 50%, and that it is more likely a combination of both increased BMD and reduced bone turnover.

Bone turnover markers may be a better measure of response to treatment. Urinary markers have a maximum suppression in the order of 50% within three months of starting therapy, compared with a two year time frame before a lack of response is noted using BMD, and are also easier and less costly to measure.

3. Prognosis

Osteoporosis affects 1 in 3 women and 1 in 12 men aged over the age of 50. It is estimated to cause over 200,000 fractures in the UK each year (over 40,000 spinal fractures, 70,000 hip fractures and 50,000 wrist fractures). High-risk groups include the elderly, those who have taken long-term corticosteroids, women who have had an early menopause or have had their ovaries removed, those who smoke or have a low body mass index, and those with a family history of osteoporosis.

In the UK, estimates of the annual cost of osteoporosis to the NHS vary from £940 million (RCP, 1999) to £1.8 billion (Burge *et al*., 2001). Hip fractures, which can have

a profound detrimental effect on quality of life account for more than 20% of orthopaedic bed occupancy, with the cost of surgical replacement estimated to be around £4,800 per patient. One in five people experiencing a hip fracture require long-term residential care (costing £19,000 per year), and one tenth to one fifth of women die within the following year (Soloman, 2002), which equates to approximately 14,000 people in the UK annually (NSF, 2001a).

More than one-third of adult women will sustain at least one osteoporotic fracture during their life. A 50 year old white woman has a risk of hip fracture during her remaining lifetime of about 16%, and of vertebral fracture of 32% (Cummings *et al*., 1989). Most women over 70 have osteopaenia. Over 80, most have osteoporosis and 90% will have suffered a fracture. The most common fractures include vertebral compression fractures and fractures of the distal radius (wrist) and proximal femur (hip).

4. Setting of care

Osteoporosis is a condition that can in theory be managed in primary care, but is plagued by an inappropriate number of referrals to secondary care services. A survey conducted in 1986 found that 20% of general practitioners claimed they had never seen a case of osteoporosis among their patients (Edwards and Fraser, 1997), while research from the few specialists in osteoporosis at that time indicated to the contrary that osteoporosis was a major problem. Disease awareness campaigns aimed at educating primary care have been only moderately successful, as many GPs continue to refer patients to secondary care specialist clinics.

Case-finding exercises do take place in primary care. Specialist nurses search through patient records to identify people at particular risk of osteoporosis and then offer them a consultation. Had clinical indicators for osteoporosis been included in the Quality Outcomes Framework section of the General Medical Services Contract introduced in 2004, it may have gone some way to recognising the importance of the primary care setting in the prevention of osteoporotic fractures.

5. Disease Management

Management of osteoporosis is divided into treatment and prevention:

- *Treatment* involves increasing bone mass in patients with osteoporosis to prevent further fractures. Can also be referred to as:
    - ‘secondary prevention’ if a patient has already sustained a clinically apparent (i.e. symptomatic) osteoporotic fracture; or
    - ‘primary prevention’ in patients with osteoporosis based on a T-score of -2.5, but with no clinically apparent osteoporotic fractures.

- *Prevention* involves increasing bone mass in patients without osteoporosis (but are at high risk) to prevent osteoporosis from developing. Can also be referred to

as 'primary prevention' but of *osteoporosis*, as opposed to primary prevention of *fracture* in patients with diagnosed osteoporosis.

In clinical practice this distinction is less appropriate, since all BPs act through inhibition of bone resorption.

Fractures can be prevented both through pharmacological intervention and lifestyle modification. In addition to BPs, other pharmacological therapies shown to increase bone mass include:

- Hormone Replacement Therapy (HRT)[40] – oestrogen replacement to prevent bone loss in to women entering menopause/men with low testosterone
- Calcitonin (thyroid hormone) - inhibits bone resorption and reduces pain associated with fractures
- Dietary supplements (calcium and vitamin D) – vitamin D is essential to absorb calcium from food and regulates bone resorption. Calcitrol is the active form of vitamin D
- Anabolic steroids - increase bone and muscle mass. Reserved for the very elderly due to side effects
- Sodium Fluoride – increases vertebral bone density but concerns that bone was structurally flawed and weaker limited its use.
- Selective Oestrogen Receptor Modulators (SERMS) – mimic effects of oestrogen (raloxifene)
- Parathyroid hormone (Teriparatide) - stimulates production of new bone.

At the time the interviews with the Industry took place, NICE had produced guidance on the main pharmacological therapies for the secondary prevention of fractures in osteoporosis (NICE, 2005). NICE guidance (2005) states:

"BPs are recommended as treatment options for the secondary prevention of osteoporotic fragility fractures:

- In women aged 75 years and older, without the need for DEXA scanning
- In women aged between 65-74 if presence of osteoporosis confirmed by DEXA scanning (treatment can be commenced prior to scanning provided a scan is booked)
- In postmenopausal women younger than 65 if they have:
    - low BMD (T-score $\leq$-3 SD)
    - confirmed osteoporosis plus $\geq$1 additional age-independent risk factor:
        - low body mass index
        - family history of maternal hip fracture before the age of 75 years
        - untreated premature menopause
        - medical disorders independently associated with bone loss
        - conditions associated with prolonged immobility.

[40] Withdrawn as a first-line option for prevention in 2003 due to concerns regarding long-term safety.

- In their choice of BP, clinicians and patients need to balance the drug's overall proven effectiveness profile against tolerability and adverse effects in individual patients.
- Raloxifene and teriparatide are recommended as second-line therapies to BPs".

NICE have since published guidance on interventions for the primary prevention of fragility fractures (NICE, 2008a), which recommends alendronate as first-line therapy, with risedronate and etidronate reserved as alternative treatment options. At that time, the guidance stated that recommendations for the primary prevention of osteoporosis in women with osteopaenia or normal BMD would be made in future guidance produced by NICE. NICE guidelines on osteoporosis were finally published in August 2012, nine years after publication of the scope.

6. Pharmacological Mechanism

BPs are effective antiresorptive agents. They are stable synthetic analogues of naturally occurring inorganic pyrophosphate (an endogenous regulator of bone turnover), but unlike pyrophosphate, BPs are resistant to breakdown by enzymatic hydrolysis. BPs have a high binding affinity for hydroxyapatite (HA), a calcium-phosphate complex that is the primary mineral component of bone, due to the presence of a P-C-P bond. The different drugs within this class have different side chains attached to the P-C-P bond which determine the different potencies and degrees of absorption from the bowel. Despite poor absorption from the bowel, BPs localise preferentially in bone and persist for several months to provide a prolonged period of action.

BPs adsorb to the surface of bones and are internalised by the osteoclast cell during the resorption process. The osteoclasts adhere normally to the bone surface but do not show the ruffled surface that indicates active resorption. The non-nitrogen containing BP (etidronate) effectively poisons the osteoclast by becoming substituted into ATP and disabling ATP dependent-enzymes. The more potent nitrogen containing BPs (alendronate and risedronate) disable enzymes of the mevalonate pathway. By inhibiting osteoclast activity, shallow pits are left allowing osteoblasts to increase bone mass.

7. Licensed Osteoporosis Indications[41]

Etidronate

Cyclical etidronate (Didronel PMO) is an oral BP licensed for:

- treatment of osteoporosis and the prevention of bone loss in postmenopausal women.
- prevention and treatment of corticosteroid-induced osteoporosis.

Didronel PMO therapy is a long-term cyclical regime administered in 90-day cycles to correspond with the osteoclast-osteoblast cycle. Each cycle consists of etidronate 400mg for the first 14 days, followed by calcium 500mg for the remaining 76 days. Due

[41] Based on the British National Formulary indications.

to poor gastrointestinal absorption, etidronate has to be taken on an empty stomach an hour before, or two hours after meals.

Etidronate was initially licensed for Paget's disease in the UK in 1987 , but it soon became apparent that if given continuously at high doses, etidronate could result in impaired mineralisation (osteomalacia – see section on long-term effects). This problem was avoided when etidronate was launched for osteoporosis by using low dose intermittent therapy incorporated into a calcium-containing cyclical regimen. In 2003/2004, 23% of prescriptions for BPs in England were for etidronate (NICE, 2005). It still has a reasonable market share as it was the first of the BPs to become generically prescribed, but it has lower efficacy compared with alendronate and risedronate.

Alendronate

Alendronate is an oral aminobisphosphonate licensed for the:

- treatment of postmenopausal osteoporosis (10mg daily or 70mg once weekly), and osteoporosis in men (10mg daily).
- prevention of postmenopausal osteoporosis (5mg daily)
- prevention and treatment of corticosteroid-induced osteoporosis (5mg daily)

In 2003/2004, 61% of prescriptions for BPs in England were for alendronate (NICE, 2005).

Risedronate

Risedronate is an oral pyridinyl bisphosphonate licensed for:

- treatment of postmenopausal osteoporosis to reduce risk of vertebral and hip fracture: 5mg daily, or 35mg once weekly.
- prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women: 5mg daily.

The once weekly formulation was launched two years after alendronate's weekly formulation. In 2003/2004, 16% of prescriptions for BP in England were for risedronate (NICE, 2005)

8. Safety and Regulation

8.1. Acute upper gastrointestinal side effects

The major safety issues that have plagued the BP class are upper gastrointestinal (GI) side effects that present as oesophageal ulceration. The problem mainly affects alendronate, but the other BPs may have also been implicated through class association. The presence of the nitrogen-containing side arm in the aminobisphosphonates (alendronate and risedronate) can irritate the upper GI mucosa if there is prolonged local mucosal exposure to the drug, hence the need for such complex dosing instructions. The

study that prompted the release of a 'Dr Doctor' letter from MSD (de Groen *et al*., 1996) did highlight that the findings of the post-marketing surveillance study were not consistent with those reported in clinical trials, where no significant differences were observed between alendronate and placebo. They stated that the difference was most likely due to the controlled environment of clinical trials, where close monitoring and reinforcement of correct administration can take place (de Groen *et al*., 1996). This was supported by a re-examination of the data in the Fracture Intervention Trial (FIT 1) using the same criteria of oesophageal irritation as used by de Groen *et al.* (1996), which showed no evidence of an increased incidence of serious or severe adverse effects compared with placebo (Liberman and Hirsch, 1996). Soon after the MSD letter, P&G released a statement stressing that in 18 years of post-marketing surveillance, only one case of oesophageal ulceration and five cases of oesophagitis had been associated with Didronel PMO (Procter & Gamble, 1996).

8.2. Long-term effects

Bone age:
There is a concern with all BPs that long-term suppression of bone remodelling may alter the material properties of bone. The bone age effectively increases, which may affect its mechanical integrity over time and potentially contribute to the risk of developing atypical fractures.

Osteomalacia:
Etidronate was the only BP that was associated with osteomalacia. Osteomalacia, which means 'soft bones', occurs when newly formed bone does not mineralise. It was more of a concern for etidronate's initial indication of Paget's disease as the dose required to inhibit resorption was very close to that which could inhibit normal skeletal mineralisation. The dose was reduced for the osteoporosis indication, but perceptions of the drug may still have been affected. Other BPs were not associated with this condition as they could be used at much lower doses due to their higher potency.

Osteonecrosis of the jaw
This safety issue only became apparent after the interviews had taken place. Bisphosphonate-related osteonecrosis of the jaw is defined as exposed, necrotic bone in the maxillofacial region that persists for more than eight weeks in current or past recipients of BP therapy. The condition can occur spontaneously or after invasive dental procedures. In September 2009, the European Medicines Agency completed a review and concluded that there was an increased risk of osteonecrosis of the jaw in patients using these medicines**.**

8.3. HRT withdrawal

Following the publication of two major studies assessing the long-term effects of HRT; The Women's Health Initiative (WHI) trial of oestrogen plus progestin (2002) and the Million Women Study (2003), the UK Committee on Safety of Medicines concluded in December 2003 that despite its effectiveness in preventing osteoporosis, the balance of

risks and benefits was such that HRT should no longer be considered as a first-line therapy due to the increased risk of breast, endometrial and ovarian cancers in a duration-dependent manner.

9. Efficacy

All three BPs are effective in preventing vertebral fractures, but alendronate and risedronate are also effective in reducing hip fracture. In lieu of interventional studies of etidronate's effect on hip fracture, NICE guidance (2005) acknowledged that although an effect was likely, it would be less pronounced than with alendronate and risedronate. Previous vertebral fracture and low BMD (T-Score <-2.5) at the femoral neck (even in the absence of previous fracture (Cummings *et al*., 1998)) identified those osteoporotic women who benefitted from treatment.

Table A13.2: Summary of fracture risk reduction and BMD increases for bisphosphonates in pivotal clinical trials

Bisphosphonate	Relative Risk Reduction (RRR) of Fracture[42]		Increase in BMD	
	Vertebral	Non-vertebral	Vertebral	Non-vertebral
Etidronate	-	-	4-8%	2-4%
Alendronate	44-48%	55%	6-8%	4-8%
Risedronate	41-49%	33-40%	4-6%	3-6%

Table A13.3: Evidence for the efficacy of therapies in osteoporosis (WHO Technical Report Series 921)

Intervention	BMD	Vertebral fracture	Non-vertebral fracture	Hip fracture
Etidronate	A	B	D	D
Alendronate	A	A	A	A
Risedronate	A	A	A	A
Calcium	A	B	B	D
Calcium + vitamin D	A	-	A	A
Raloxifene	A	A	-	-
Oestrogens	A	A	A	A
Calcitonin	A	C	C	D
Fluoride	A	C	-	-
Anabolic steroids	A	-	-	D

Evidence A: positive evidence from one or more adequately powered, randomised controlled trial; B: positive evidence from smaller non-definitive randomised controlled trials; C: inconsistent results from randomised controlled trials; D: positive results from observational studies; -: efficacy not tested.

[42]Calculated from relative risk (RR). RR=1: no difference; >1: increased risk in group exposed to treatment; <1: reduced risk in group exposed to treatment. e.g: RR of 0.4 equates to a relative risk reduction of 60% (1-RR). RR of 1.38 equates to a 38% increased risk.

9.1 Trial design - clinical outcomes

Ideally trials in this disease area would only look at fracture rates and not surrogate markers, but it is often a case of pragmatism. A trial involving up to 30,000 patients would be required to provide sufficient power to demonstrate a comparative difference between different BPs in terms of fracture reduction.

Fracture reduction:

- Trial results were frequently presented as relative risk reductions (RRR), which can appear substantial, but when considered as an absolute risk reduction (ARR) the numbers are small (e.g. in FIT 1 (Black *et al*., 1996) a RRR of 51%, corresponded to an ARR of just 1.1%).

- Vertebral fractures are important because they predict subsequent non-vertebral fractures independently of BMD (see section on diagnosis). Some studies used clinical (i.e. symptomatic) fractures as their endpoint, while others used fractures that were identified radiographically (sometimes called morphometric), which include symptomatic and asymptomatic fractures.

- If facture is used as an endpoint, then trials tend to recruit women with multiple vertebral fractures at base line and are therefore at very high risk of developing subsequent fractures. However, the applicability of the results of these trials to the general population with osteoporosis may then be limited. In the FIT 1 trial (Black *et al*., 1996), the primary endpoint was numbers of women with fractures rather than the total number of fractures to attempt to avoid these statistical issues.

- In treatment studies, the higher risk of fragility fracture occurring in study populations enables the assessment of anti-fracture efficacy. Prevention studies however are performed in early postmenopausal women with osteopaenia or normal BMD, in whom the absolute risk of fragility fracture is low within the 1-2 year study period, and therefore does not allow for assessment of anti-fracture efficacy to be tested.

BMD:

In clinical trials, BMD was measured at various vertebral and non-vertebral sites which made direct comparisons difficult. Vertebral sites included the lumbar spine and lateral spine. Non-vertebral sites often included several hip locations (femoral neck, femoral trochanter (upper part of the femur), total hip), wrist (distal radius), forearm (mid-shaft radius), pelvis, total body, leg and clavicle, but occasionally non-vertebral results would be pooled.

9.2. Volume of evidence

Searches of the biomedical literature databases (Table A13.4) indicated substantially more clinical studies produced for alendronate compared with etidronate that had been on the market for a longer period of time. In the three years following launch when a technology can still be considered to be new (Linden *et al.,* 2007), the relevance of clinical trials assumed more importance than for the first BP etidronate, potentially to support claims of differentiation.

Table A13.4:Bisphosphonates: volume of evidence: MEDLINE and EmBASE searches

BPs	No. of studies included on MEDLINE/EmBASE Databases (restricted to clinically sound[43] studies)		
	From launch to terminal curve date (year ending 2004)	3 years before launch	3 years post-launch
Etidronate	25	2	3
Alendronate	54	2	9
Risedronate	18	3	8

10. Guidelines:

The need for guidelines was realised in the mid 1990's, following a change in the definition of osteoporosis by the WHO in 1994. Changes to policy were then necessary in response to the recommendations.

WHO

The WHO redefinition was in response to a consensus development conference that had convened in Rome in 1992 following recognition by the WHO that views on the assessment and treatment of osteoporosis were not consistent amongst experts. At the meeting, experts proposed expanding the definition of osteoporosis, from that of an elderly person with a fracture, to anyone who had a BMD T-Score of $\leq$ - 2.5, and in doing so, also created the term osteopaenia to describe a pre-osteoporotic state (Sandor *et al*., 1998). The WHO has been involved in many initiatives to raise awareness of osteoporosis, promote preventative and management strategies and increase its priority on the worldwide political agenda.

Department of Health Advisory Group on Osteoporosis

Following pressure from patient organisations, most notably the National Osteoporosis Society, the then Health Minister, Baroness Cumberlege established an Advisory Group on Osteoporosis in 1993 chaired by Professor David Barlow. Their remit was to ascertain what information about osteoporosis was available, what research was being conducted, and what further work needed to be done. Such attention from Government

[43]Definition of 'clinically sound' in accordance with the Health Information Research Unit (HIRU) MEDLINE and EmBASE Clinical Queries filters derived from work by Haynes *et al*., 1994.

was important in raising awareness of the condition. The group reported in November 1994 (Barlow, 1994) and recommended the establishment of local bone scanning facilities for at risk women, consideration of the role of diet as a preventative strategy, and the preparation of prevention and treatment guidelines, which led to the production of the Royal College of Physicians guidelines published in 1999.

Royal College of Physicians Guidelines:
When the authoritative Royal College of Physicians Guidelines on the prevention and treatment of osteoporosis were produced in 1999, etidronate, alendronate and raloxifene were licensed, so they were able to provide guidance on the basis of cost effectiveness and there was a clear template as to how osteoporosis services and intervention should be approached based on the WHO definition.

Several other major policy documents and guidelines followed, but their impact is questionable as osteoporosis was often only included as a subclause of the wider issue of falls in older people, they were produced late on in the lifecycles of the bisphosphonates, and any reference to pharmacological interventions were generally limited, and/or did not differentiate between drugs within a class (notable examples are listed in the BP timeline commentary for secondary level evidence and guidelines).

11. Policy issues - Fracture Service Provision

Access to bone densiometry services in the UK was slow to develop, despite osteoporosis being acknowledged as a major public health problem. In a national survey conducted by the National Osteoporosis Society in 1995, only 13 health authorities were providing services that met DH recommendations. The vast majority provided no funding for bone densiometry. A further survey conducted in 2000 (Rowe and Cooper, 2000) showed a 60% increase in the number of health authorities contracting for DEXA scans. There continued to be wide variation in service provision, attributed by the authors to the disorganised way in which fracture services developed, with variable levels of funding for osteoporosis diagnostic services that resulted in inequitable access.

Industry needed patients to be diagnosed in order that they can be treated and saw an opportunity to become involved through the development of Fracture Liaison Services (FLS), which was synchronous with the release of the once weekly formulation of alendronate. FLS optimise selective case-finding of patients who have already experienced a fragility fractures. Specialist nurses liaise between secondary care bone metabolism services and the orthopaedic and A&E departments to ensure all patients over 50 with fracture are identified. The first FLS was established in Glasgow in 1999, and by 2003, the British Orthopaedic Association advocated the implementation of the FLS model on a national basis (Merck Sharp & Dohme, 2005). In 2005, the DH announced investment of £20 million to improve access to DEXA scanning, but the funding was not ring-fenced for this purpose and there has continued to be wide variation in service provision.

Osteoporosis clinical indicators were not included in the original Quality and Outcomes Framework when it was first introduced in 2004. Following review, they were added

from April 2012 to ensure patients over the age of 50 who sustain a fracture are assessed for osteoporosis.

11. Cost

At the time of alendronate's introduction, it cost double that of cyclical etidronate and it was not clear if its effectiveness was greater than etidronate due to the lack of head to head data. The cost of risedronate on entry to the marker was similar to alendronate. When NICE assessed cost effectiveness, the average cost per QALY for each treatment at age 65 in women at the threshold of osteoporosis with a previous fracture was £24,777 for alendronate, £29,127 for risedronate and £58,916 for etidronate (or £34,018 when observational data on hip and wrist fracture was included).

Appendix 14: Background literature on atypical antipsychotics for schizophrenia

1. Schizophrenia

Despite its relatively low incidence (15.2/100,000), the prevalence of schizophrenia is relatively high, with nearly one in 100 people in Britain affected. This is because the disorder often presents in late adolescence or early adult life and becomes chronic (Saha *et al*., 2005). In Britain, around 35,000 people enter hospital with this illness each year. Mean length of stay is around 130 days with a median duration of 30 days (NICE, 2002b). It is estimated that the cumulative cost of care of individuals with schizophrenia accounts for 1.6% of the total national health care budget and 5.4% of NHS inpatient cost (Davies and Drummond, 1990; Knapp *et al*., 2002).

Schizophrenia is a multifactorial, spectrum disorder. The aetiology remains poorly understood, but the greatest risk factor is a positive family history. Schizophrenia can follow a relapsing and remitting course, or it can be chronic and progressive. The condition manifests as positive and negative symptoms; positive symptoms relate to an exaggeration of normal functions which are a consequence of malfunctioning of the dopamine system; negative symptoms relate to the loss of normal functions (Picchioni and Murray, 2007).

Symptoms of Schizophrenia

Positive symptoms:

- *Lack of insight – failure to appreciate symptoms are not real or caused by illness*
- *Hallucinations – auditory most common, but can include touch, smell taste or vision*
- *Agitation*
- *Delusions*
    - *Persecution: believe being victimised or central to a conspiracy*
    - *Passivity: thoughts/actions controlled by an external force*
    - *Other: grandiose, sexual or religious*
- *Thought disorder – distorted or illogical speech*

Negative symptoms:

- *Social withdrawal; self neglect; loss of motivation and initiative; emotional blunting; paucity of speech*

2. Diagnosis

Patients can present with a range of complex symptoms including anxiety and depression, difficulties in concentrating etc. that can be initially confused with other conditions. However, a diagnosis of schizophrenia is based on the following ICD-10 diagnostic criteria:

At least **one** present most of the time for a month:

- Thought echo, insertion or withdrawal, or thought broadcast
- Delusions of control referred to body parts, actions or sensations
- Delusional perception
- Hallucinatory voices
- Persistent bizarre or culturally inappropriate delusions

Or at least **two** present most of the time for a month:

- Persistent daily hallucinations accompanied by delusions
- Incoherent or irrelevant speech
- Catatonic behaviour
- Negative symptoms such as marked apathy or incongruous mood

3. Prognosis

Some individuals with schizophrenia have predominantly acute episodes associated with little long-term impairment. Studies suggest that about 20% recover, 70% have relapsing disease and about 19% are seriously disabled by the disease (Robinson *et al*., 1999).

4. Setting of care

If the onset of psychosis is suspected, the patient is rapidly referred to secondary care for diagnosis and initiation of treatment. The vast majority of people with a diagnosis of schizophrenia in the care of the NHS (about 85-90%) are treated by secondary care mental health services, which in the UK consists of local early intervention or home treatment teams, or the community mental health team. The need for hospital admission and the use of the Mental Health Act is dependent on the patient's presentation, the risk assessment and availability of good community support. Only 10-15% of service users are managed solely in primary care (NICE, 2002b). However, GPs are increasingly being asked through the QOF to have a role in monitoring, as the association between schizophrenia and poor physical health is well established (Phelan *et al*., 2001).

5. Disease management

Despite the fact schizophrenia is not curable, there are treatment options that help to suppress the symptoms. Following a diagnosis, first-line treatment is with an oral antipsychotic, unless the patient is non-compliant and experiencing an acute manic episode, in which case a depot intramuscular formulation may be more appropriate due to its rapid onset of action.

NICE guidance (2002a) recommends that:

- AAs for new patients should be considered *within* the choice of first-line treatments for patients with newly diagnosed schizophrenia.
- In patients on conventional antipsychotics (CAs) with adequate symptom control, but with unacceptable side effects, or for those in relapse who have previously experienced unsatisfactory management with CAs, then AAs should be considered.
- Patients on CAs with good control of their condition, without unacceptable side effect control should not be switched to AAs.

Most side effects of antipsychotics are dose related and therefore the lowest efficacious dose for the individual patient should be used. Following recovery from an acute episode of schizophrenia, prophylactic doses of antipsychotic for one to two years is recommended, whilst continuing to be supervised by specialist services (NICE, 2002a). If the patient is well and symptom free, the dose is gradually reduced with careful monitoring achieved by collaboration between primary and secondary care to detect any signs of relapse. Concurrent use of two or more antipsychotics is however limited to specialist services.

Several health professionals other than psychiatrists are involved in making treatment decisions in patients with schizophrenia e.g. community psychiatric nurses, but the rising importance of drugs and therapeutic committees, and the role of payers has restricted access to the selection of drugs that can be prescribed. In addition to pharmacological therapy, several psychological treatments are used to help ameliorate symptoms.

6. Pharmacological mechanism

The AAs differ pharmacologically from previous antipsychotic agents in their lower affinity for dopamine D_2 receptors and greater affinities for other neuroreceptors, notably those for serotonin (5-hydroxytryptamine (5HT) $_{1A}$, $_{2A}$, $_{2C}$, $_{3}$, $_{6}$ and $_{7}$) and norepinephrine (α_1 and α_2) (Miyamoto *et al*., 2005).

It has been suggested that both activity, and absence or presence of EPS side effects is related to the delicate balance required in binding affinity for dopamine receptors. Molecularly, CAs bind to dopamine receptors more tightly than even dopamine itself and so are released slowly. The AAs however, bind loosely and so can rapidly disassociate from the receptors. If the binding is loose then there is virtually no EPS, but

if it is too loose the antischizophrenic activity is lost. CAs block up to 80% of D_2 receptors, while clozapine and quetiapine block around 30%, which may explain their lower propensity to cause EPS. Leaving the D_2 receptors unoccupied for periods of time, allows the natural dopamine system to operate more effectively and so negative symptoms are less likely to occur with AAs. The role of serotonin is less clear as 5HT binding is not a prerequisite for clinical efficacy of atypicals.

7. Historical context

7.1 Conventional Antipsychotics (first generation)

The conventional or typical antipsychotics (CAs) such as chlorpromazine and haloperidol have been essential in treating schizophrenia since they were first introduced in the 1950s. These drugs target the dopamine D_2 receptors in the brain and their effectiveness in reducing the intensity of patients' delusions and hallucinations not only suggested for the first time that schizophrenia had a biochemical basis, but permitted outpatient treatment instead of lifelong institutionalisation (Freedman, 2005).

CAs are associated with significant side effect issues. Extrapyramidal effects, of which tardive dyskinesia (TD) which is the development of involuntary movements initially of the face, lips and tongue, but eventually affecting other parts of the body, is a particular concern and persists even after treatment discontinuation. It occurs in around 20% of people receiving CAs after chronic use (>6 months) (Kane *et al.*, 1985). Other side effects include sedation, hyperprolactinaemia, reduced seizure threshold, postural hypotension, anticholinergic effects (blurred vision, dry mouth), neuroleptic malignant syndrome, weight gain, sexual dysfunction and cardiotoxicity (prolongation of QTc interval).

A particular issue with schizophrenia is that if patients experience such severe adverse effects on the first-line approach to treatment, then their insight compliance is so marginal they may give up on treatment altogether. The side effects of CAs contribute to rates of non-compliance amongst patients approaching 50% (Tollefson *et al.*, 1997), which is a major cause of relapse and rehospitalisation.

Around one third of patients with schizophrenia are also unresponsive to CAs (Conley and Buchanan, 1997), so the early promise of these drugs was only partially fulfilled. They were highly effective but not very well tolerated in most cases. Effects on modest doses were limited and there was a reluctance to switch onto other CAs, for although they were not a class, they were perceived by clinicians as all acting in the same way. The only option therefore was to increase the dose further in lieu of not being able to offer anything else. By the early 1980s, megadoses several orders of magnitude greater than BNF limits were being tested as a means of controlling symptoms in people who would otherwise be considered treatment-resistant (Aubree and Lader, 1980).

From a patient perspective, these drugs were also becoming very unpopular. The very high doses being administered were resulting in significant adverse effects that were not being outweighed by the benefits, particularly when some of these patients were compelled to take the drugs through the Mental Health Act. All these factors together

translated into a significant clinical need for something new that psychiatrists could offer to patients, and this need continued to build for several decades until the AAs were introduced. CAs are still available, but are now limited to specialised uses.

7.2 Atypical Antipsychotics (second generation)

The term 'atypical' was first applied to clozapine (Clozaril, Novartis) in 1988 following a pivotal study that demonstrated its unusual behaviour in patients resistant to chlorpromazine (Kane *et al.*, 1988). It has since been applied broadly and uncritically to antipsychotic drugs marketed since then despite their chemical, pharmacological and clinical heterogeneity (Gardner *et al.*, 2005). The essence of 'atypicality' remains unknown and so the parameters for the separation of atypicals from typicals is still not clearly defined or agreed.

Clozapine is the most efficacious of all antipsychotics, but is restricted to treatment-resistant schizophrenia because of its adverse effect profile. Therapeutic difference between the other AAs and CAs is less certain, with differentiation based on their side effect profiles. AAs have a lower propensity to cause EPS, and with minimal stimulation of prolactin release (Jones *et al.*, 2006).

Clozapine – the first atypical antipsychotic

By the early 1970s, experience with clozapine suggested that it might be significantly more effective than CAs. It appeared to improve the negative symptoms of schizophrenia in addition to the positive symptoms and was almost devoid of EPS. However, problems soon emerged as it became associated with a high risk of agranulocytosis (a potentially fatal reduction in white blood cells), seizure and orthostatic hypotension and was voluntarily withdrawn in 1975 for a period of time.

Even at that time, there were indications that clozapine acted differently to CAs and seemed to improve symptoms in patients who were severely ill or refractory to treatment. Following pressure from psychiatrists to reintroduce clozapine, its undisputed efficacy in refractory patients was demonstrated in a landmark trial by Kane *et al.* (1988). The trial, which showed a 30% response rate to clozapine, compared to a 3% response to chlorpromazine in patients who were refractory to haloperidol, led to clozapine's reintroduction on a limited second-line basis in the early 1990s. This was on the proviso patients were subject to regular haematological monitoring through the nationally coordinated Clozaril Patient Monitoring Service (provided by Novartis) under control of a specialist consultant psychiatrist.

Clozapine was only ever licensed in the UK as a second-line therapy, initially for people with resistance to CAs, but also now in those refractory to other AAs, which accounts for around 10% of patients (Freedman, 2005). Clozapine was regarded as a good molecule, but for schizophrenia where there is a correlation between response to treatment and insight and adherence, the perception of risk which far outweighed the actual risk, and its limitations in terms of monitoring were a disincentive for many patients and clinicians and produced a barrier to its uptake and diffusion.

Clozapine was not an option for the vast majority of people with schizophrenia and coupled with clinicians' dislike for the CAs, this presented an opportunity for the pharmaceutical industry to develop new variants that attempted to capture the enhanced therapeutic effect of clozapine without its toxicity. The perception of risk associated with the use of clozapine however, potentially made for a sceptical market in which to launch a new AA. The first of these was risperidone, followed closely by olanzapine, quetiapine and several others.

Risperidone

Risperidone (Risperdal, Janssen-Cilag) was the first AA to be released after clozapine in 1993. It is a benzisoxazole derivative, chemically unrelated to any other antipsychotic currently available. It was first introduced as an oral tablet, but has since been launched in various other formulations. It is licensed for schizophrenia and moderate to severe manic episodes associated with bipolar disorder. In schizophrenia, the initial dose is 1mg daily which can be titrated slowly to 2mg twice daily over a 1 week period. The usual dose range is 4-6mg/day, up to a maximum of 16mg daily. At launch there was some confusion over what the optimal dose was, as several of the early trials on risperidone were using doses of 16-20mg/day (Claus *et al*., 1992; Ceskova and Svestka, 1993), which was relatively high compared to those now recommended. At higher doses, risperidone showed similar effects to CAs and the degree of differentiation required to sufficiently achieve the separation from the older drugs, may not have been apparent.

Olanzapine

Olanzapine (Zyprexa, Lilly) was launched 3 years after risperidone in 1996. It is a thienobenzodiazepine derivative structurally related to clozapine, so the pharmacological profile was similar but side effects were significantly improved compared with CAs. It is licensed for schizophrenia, and the treatment of moderate to severe manic episodes, and prevention of recurrence of mania in bipolar disorder. In schizophrenia the dose is 10mg daily adjusted to a usual range of 5-20mg daily. There is no need for titration, which ultimately translated to ease of use for psychiatrists and patients.

Quetiapine

Quetiapine (Seroquel, AstraZeneca) is a dibenzothiazepine antipsychotic, structurally related to clozapine and olanzapine. It is licensed for use in schizophrenia and in the treatment of manic episodes and major depressive episodes associated with bipolar disorder. Doses range from 150mg-750mg/day, titrated upwards from 25mg twice daily from day 1 to 300 mg/day on day 4. The average dose is around 300-450mg/day.

8. Safety and regulation

Experience of market withdrawals with clozapine, remoxipride and sertindole in this class has meant that the safety of AAs has always been under close scrutiny.

8.1. Long-term effects

The AAs fulfilled their promise of causing less movement disorder, but new problematic side effects including severe weight gain, often accompanied by type 2 diabetes mellitus (Sernyak *et al*., 2002) and hypercholesterolemia (Lindenmayer *et al*., 2003), started to emerge during the early part of 2000. There is an argument that schizophrenia itself, irrespective of pharmacological intervention, is associated with increased risk of diabetes (Schimmelbusch *et al*., 1971; Dixon *et al*., 2000) and weight gain (Brown *et al*., 1999), and that these side effects also occurred with the first generation drugs, but not to the same degree.
However, the body of evidence attributing these effects to AAs has been gathering pace over the last few years and there has been a definite shift in the risk perception in schizophrenia treatment away from movement disorders to metabolic issues. Regulators never distinguished between olanzapine, but data showed it was the one most people were concerned about (Allison *et al.*, 1999; Kinon *et al*., 2001; Casey and Zorn, 2001). The AAs have also been subject to safety warnings as a result of off-label usage.

(Table A14.1) Benefits and risk of conventional and atypical antipsychotics (adapted from Gardner *et al.*, 2005)[44]

		AA				**CA (by potency[45])**	
Property		Clozapine	Olanzapine	Quetiapine	Risperidone	High	Low
Efficacy in terms of	Positive symptoms	++++	+++	++	+++	+++	+++
	Negative symptoms	++	+	+	+	+	+
Adverse effects	EPS	0	+	0	++	++++	++
	Hyperprolactinaemia	0	+	0	++	++	++
	Weight gain	+++	+++	++	+	0	++
	Type 2 diabetes	++	++	+	+	+	+
	Anticholinergic	+++	+	0	0	0	+++
	Sexual dysfunction	++	++	+	++	++	+++
	Hypotension	+++	++	++	+++	+	+++

9. Efficacy

This class of drugs is assessed to a greater extent on their side effect profiles rather than efficacy which are all closely aligned in terms of effectiveness.

Table A14.2 summarises the quantity of evidence produced for each drug from launch up until 2007 and for the initial periods pre- and post-launch. Of the four case studies, this class has generated the most studies, which could be related to the fact that more evidence may be necessary to justify differentiation based primarily on side effect claims as opposed to efficacy

[44] Benefit or risk: ++++ = very high, +++ = high, ++ = moderate, + = low, 0 = negligible.
[45] Example of high potency is haloperidol; low potency chlorpromazine

Table A14.2: Atypical antipsychotics: volume of evidence: MEDLINE and EmBASE searches

AA	No. of studies included on MEDLINE/EmBASE Databases (restricted to clinically sound studies)		
	From launch to terminal curve date (year ending 2007)	3 years before launch	3 years post-launch
Risperidone	214	3	21
Olanzapine	210	0	19
Quetiapine	67	4	6

The majority of trials are Industry sponsored, which is unsurprising as psychiatry is often referred to as a 'Cinderella specialty' due to relatively few funding charities. This results in a greater need for Industry to fund activities such as trials and continuing professional development than in other larger specialties such as cardiology.

10. Policy and Guidelines

AAs are usually grouped as a class in clinical guidelines despite their heterogeneity, and as such, there has been no attempt to distinguish between them. Several guidelines indicated that AAs should be the first choice in treatment, particularly those produced in the USA which can influence practice in the UK. NICE guidance, which is mandatory in England and Wales, would not distinguish between the atypicals, but stated they should be considered *within* first-line treatment, not considered *as* first-line treatment as some marketing has suggested. In April 2002, just prior to publication of the technology appraisal, Janssen-Cilag attempted to use the data from their long-term study (Csernansky *et al.*, 2002) to appeal NICE guidance (2002a), so as to place risperidone as the first choice amongst the AAs. NICE however rejected the appeal on the grounds that they regarded the AAs as a class and not individual technologies (NICE, 2002a).

Several other major policy documents that relate to mental health have been produced, including the National Service Framework for Mental Health (Department of Health, 1999b) and the Government White paper: Saving Lives: Our Healthier Nation (Department of Health ,1999a). Their impact however was limited as they mainly dealt with service issues in mental health, setting out national standards; national service models; local action and national underpinning programmes for implementation, and little if anything about pharmacological intervention.

11. Cost

The emphasis on cost pressures is far more apparent now than when these drugs were first introduced. At that time, it was more a case of safety at any cost if it meant that patients were spared from the risk of TD. Now that there is some doubt over their effectiveness compared with CAs, this has led people to question their value through extensive large scale comparator trials (CATIE/CUtLASS1). The higher acquisition cost of olanzapine relative to risperidone is unlikely to be offset by clinically significant differences in efficacy or safety, which has been represented in a slowing in the uptake rate since 2004.

Appendix 15: Background literature on phosphodiesterase type 5 (PDE5) inhibitors for erectile dysfunction

1. Erectile dysfunction (ED)

The term 'erectile dysfunction' (ED) was first recorded in MEDLINE in 1980 (Tordjman *et al*., 1980), several years in advance of the development of PDE5 inhibitors, but the wider recognition of this term used in the marketing of sildenafil was instrumental in changing the perception of the disease. Risk factors include advancing age, with the condition becoming increasingly common in men over 40 years; the presence of chronic illness (heart disease, hypertension, diabetes mellitus, depression); smoking; stress; alcohol; drug abuse and a sedentary lifestyle. While sometimes considered pejoratively as a 'life-style' disorder, ED significantly impacts on patients' quality of life, psychological health and relationships.

The World Health Organization (WHO), and British, European and American guidelines on ED recommend that oral therapies, predominantly PDE5 inhibitors should be used as first-line treatment for ED (Jardin *et al*., 2000; Ralph and McNicholas, 2000; Hackett *et al*., 2008; Wespes *et al*., 2002 and 2006; Montague *et al*., 2005). Prior to their introduction, therapies included transurethral delivery, intracavernosal or intraurethral injections of vasoactive substances such as alprostadil; penile implants or vacuum constriction devices as mechanical aids; or venous or arterial surgery (Goldstein *et al*., 1998).

2. Diagnosis

ED is believed to be highly prevalent and often undertreated due to the stigma associated with the condition. Studies in men between the ages of 16-78 in the UK indicate a prevalence of around 19%, which equates to over 4 million men (Goldmeier *et al*., 1997). This figure is supported by the Men's Attitudes to Life Events and Sexuality (MALES) study that assessed the prevalence of ED in nearly 28,000 men aged between 20-75 years across 8 countries, indicating a UK prevalence of 13% (Rosen *et al*., 2004). The prevalence in adult diabetic men is 35%, rising to >60% in men over 60 years of age, with smoking doubling the prevalence of ED in men with diabetes or heart disease (Feldman *et al*. 1994). The introduction of sildenafil, the first oral therapy for ED, significantly helped to overcome the taboo associated with ED that had prevented men coming forward for treatment (Wright, 2006). In a UK 'before and after' study, the diagnosis of ED more than doubled following the launch of sildenafil onto the UK market in 1998 (Kaye and Jick, 2003).

ED is notoriously difficult to diagnose as it is a self-reported condition. In the year before sildenafil was launched, Rosen *et al*. (1997) developed a new diagnostic tool to assess ED called the International Index of Erectile Function (IIEF). The 15 point questionnaire based on subjective measures categorised into five domains: erectile function, orgasmic function, sexual desire, intercourse satisfaction and overall satisfaction, changed diagnosis from a binary yes or no, to that of a sliding scale, which

is believed to have impacted upon increasing the prevalence estimates of ED. In addition, all three companies were involved in non-branded education campaigns about ED, designed to educate men about the condition. This helped them become more comfortable discussing the topic and to seek treatment for their ED. Current UK guidelines base a diagnosis of ED on a combination of a detailed case history, genital and physical health examination, investigations including serum lipids, plasma glucose, and serum testosterone (to check for hypogonadism) together with serum prostate specific antigen levels if clinically indicated. Specialist investigations, such as ultrasound of penile arteries or intracavernous injection tests, are generally only indicated in patients with a history of trauma, abnormality of the testes or penis, or those that have never had normal erectile function (Hackett *et al*., 2008).

3. Prognosis

PDE5 inhibitors are effective and well tolerated drugs that not only provide an opportunity to improve the quality of life of the patient, but also that of their partner. With the many similarities in the effectiveness and tolerability of the PDE5 inhibitors, treatment decisions are heavily influenced by patient preference for the other features they offer (Wright, 2006).

The initial success rate with PDE5 inhibitors is high, but only around half of patients are still taking these drugs after one year (Althof, 2002). Several explanations have been proposed for why a disproportionately high number of individuals fail to continue using medical interventions compared to those for whom treatment is efficacious, a major one being the potential development of tachyphylaxis with continued use. In patients still taking the drugs after 2 years, around 40% required an increase in dosage to maintain efficacy (El-Galley *et al*., 2001). Alternatively, while the drugs can improve the physical issues, they may not be sufficient to resolve the co-existing psychological problems in a relationship (Althof, 2002).

Some patients fail to respond to, or are dissatisfied with, their initial choice of treatment, in which case others within the class may still be suitable. Often cases of non-response can be attributed to incorrect administration and so education and counselling can increase response rates in previous non-responders. The need for adequate testosterone levels was also highlighted by Shabsigh *et al*. (2004) when they demonstrated improved erectile function in men who had previously been unresponsive to sildenafil alone once their testosterone levels were supplemented. Guidelines recommend that patients should not be regarded as true treatment failures until they have failed to respond to a maximum dose on at least eight occasions with at least two drugs taken sequentially (Hackett *et al*., 2008).

4. Setting of care

Before the widespread use of oral drugs, ED was managed predominantly in secondary care in view of the specialist administration usually required. With orally administered therapies, the vast majority of cases could be managed within primary care. Referral

was intended only for patients unresponsive to first-line therapy or with anatomical abnormalities. However, government restrictions on prescribing of PDE5 inhibitors that followed the introduction of sildenafil inadvertently transferred a large proportion of ED patients back into secondary care for specialist determination of eligibility (see policy and guidelines sections). These regulations presented a physical barrier to access based on the sheer disparity between the numbers of specialists compared with GPs (Hackett, 2002).

5. Pharmacological mechanism

PDE5 inhibitors act to increase blood flow to the penis in response to sexual stimulation. Erections result from the local release of nitric oxide (NO) into the corpus cavernosum of the penis following sexual stimulation. NO activates the enzyme guanylate cyclase, which catalyses the formation of cyclic guanosine monophosphate (cGMP). cGMP triggers smooth muscle relaxation, allowing increased blood flow to the penile tissue.

As part of the natural feedback process, the enzyme phosphodiesterase type 5 (PDE5) then catalyses the degradation of cGMP, causing the erection to dissipate. In men with erectile dysfunction, blocking the binding site on the PDE5 enzyme with a competitive PDE5 inhibitor prevents the degradation of cGMP, enabling the erection to be maintained (Hood and Kirby, 2004).

As competitive inhibitors of the PDE5 enzyme, the structure of this class of drugs is based on cGMP. Sildenafil and vardenafil are molecularly very similar. Tadalafil, while retaining those elements required for inhibition of PDE5, is structurally different, which is reflected in its differing pharmacokinetic profile.

6. Licensed indications

- Sildenafil, tadalafil and vardenafil are all licensed for the treatment of men with ED of various etiologies (generalised and specific subpopulations).
- Sildenafil and tadalafil have been subsequently licensed for the treatment of adult patients with pulmonary arterial hypertension under the brand names Revatio and Adcirca.

<u>Sildenafil</u>

Sildenafil was initially investigated as a treatment for hypertension and angina in 1991, but the serendipitous observation that patients were reporting increases in erectile function led to a refocusing of the clinical programme towards the end of 1993 and approval of sildenafil for the treatment of ED in 1998. It quickly reached blockbuster status, expanded the ED market 10-fold, capturing nearly 95% market share (Neumeyer and Kirkpatrick, 2004). Sildenafil has become a societal phenomenon, with Viagra one of the world's most successful brands; a combination of Pfizer's marketing presence and the extraordinary mass media attention it received. Sildenafil remained

unchallenged by class competitors for five years, during which time clinicians become familiar with the drug's efficacy and safety profile (Neumeyer and Kirkpatrick, 2004).

Tadalafil (IC-351)

Tadalafil, whist maintaining a similar level of effectiveness as sildenafil, has a much longer mode of action, which addressed an element of unmet need in the ED market. This allowed the marketing angle to focus on the relationship aspect of ED, rather than just addressing the physical aspects. In doing so, Lilly avoided a head on marketing battle with Pfizer.

Vardenafil

Vardenafil was the only PDE5 inhibitor developed specifically for the treatment of ED (Neumeyer and Kirkpatrick, 2004). Despite the similarities in molecular structure, vardenafil has greater selectivity for PDE5 than sildenafil, resulting in greater potency, a faster onset of action and fewer adverse effects (particularly in relation to visual disturbances – see safety and regulation section). Efficacy however, is similar to that of sildenafil in a broad ED population, which led Bayer to target their development programme early on to demonstrate vardenafil's efficacy in difficult to treat subgroups (Neumeyer and Kirkpatrick, 2004).

A legal challenge from Pfizer against the manufacturers of tadalafil and vardenafil for exploitation of their patented research was lost in the EU, which resulted in these two drugs launching in the UK several months ahead of the USA.

7. Safety and regulation

Safety issues related to this class of drugs have been predominantly related to cardiac and sensory disturbances (visual and hearing).

Cardiovascular

Clinical trials and post-marketing data of sildenafil, tadalafil, and vardenafil have demonstrated no increase in myocardial infarction rates in patients who received these agents as part of either double-blind, placebo-controlled trials or open-label studies, or compared to expected rates in aged-matched populations of men (Kloner, 2004).

Visual and Hearing

In addition to the risk of non-arteritic anterior ischaemic optic neuropathy (NAION), other transient visual disturbances, notably a blue discolouration in colour vision have been reported, albeit rarely for sildenafil and vardenafil at high doses (Hood and Kirby, 2004). This has been attributed to their interaction with PDE6 found in the retina. Sildenafil and vardenafil are seven and three times more selective for PDE5 than PDE6, respectively, while tadalafil is over 750 times more selective (Wright, 2006). Tadalafil however, only has five-times greater selectivity for PDE11 at clinical doses. PDE11 is

found amongst other places in the smooth muscles of the internal organs, cardiac and skeletal muscles (Hood and Kirby, 2004), which may be related to the back and muscle pain occasionally reported with tadalafil (Padma-Nathan *et al*., 2001). PDE5 inhibitor product labels also had to be updated with regard to the potential risk for sudden hearing loss although no causal relationship could be established.

Common adverse effects

Common side effects of PDE5 inhibitors include headache, facial flushing, nasal congestion, and dyspepsia, which are transient and mild to moderate in nature (see Table A15.1). Tadalafil has been associated with back pain and myalgia at doses of 10-20mg.

Table A15.1: **Common adverse events of PDE5 inhibitors** - based on EMEA statements on product characteristics (Wespes *et al*., 2006).

Adverse event	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision	1.9%	-	<2%
Back pain	–	6.5%	–
Myalgia	–	5.7%	–

Contraindications

All PDE5 inhibitors are contraindicated in patients taking nitrates and those with hypotension as they potentiate the hypotensive effect. They are also contraindicated in patients with severe hepatic impairment, hereditary degenerative retinal disorders and in men whom sexual activity is inadvisable e.g. recent stroke or myocardial infarction (within the previous 6 months), unstable angina or severe cardiac failure. They can be used in men with cardiovascular disease provided they have been properly assessed and are not taking nitrates.

8. Efficacy

When the differences in efficacy and toxicity are so marginal and the outcome measures so immediately tangible (in contrast to surrogate markers), the trials likely to have an impact on diffusion are those that directly compare them. The recognisable differing pharmacological characteristics of the three PDE5 inhibitors however, has made it difficult to conduct randomised, double-blind, comparative studies, so head to head comparisons have been based on preference studies, many of which have been criticised for poor design introducing bias (Mulhall and Montorsi, 2006). One study highlighted in the British Society of Sexual Medicine guidelines (Hackett *et al*., 2008) that compared all three PDE5 inhibitors, demonstrated a preference for tadalafil based on its longer period of action (Tolra *et al*., 2006).

The EU licensing application for sildenafil included 31 phase II/III clinical studies in more than 3,000 patients. The four main studies evaluated ED in a broad spectrum population, but the comprehensively designed trial programme resulted in studies assessing the safety and efficacy of sildenafil in most of the subgroups permitted under government prescribing restrictions reporting in advance of tadalafil and vardenafil's launch: diabetes (Rendell *et al*., 1999); spinal cord injury (Giuliano *et al*., 1999); prostate cancer treated with radiotherapy (Zalefsky *et al*., 1999); spina bifida (Palmer *et al*., 2000); radical prostatectomy (Zagaja *et al*., 2000); depression (Seidman *et al*., 2001); Parkinson's disease (Hussain *et al*., 2001) and renal transplant (Prieto Castro *et al*., 2001). This then set an evidence precedent for the competing entrants.

Table A15.2 summarises the quantity of evidence produced for each drug from launch up until 2007 and for the initial periods pre- and post-launch. With the publication of nine major studies before launch, Lilly appreciated the likely need for evidence to impact on the dominance that sildenafil had on the ED market in order to change prescribing practice.

Table A15.2: PDE5 inhibitors: volume of evidence: MEDLINE and EmBASE searches

PDE5 Inhibitors	No. of studies included on MEDLINE/EmBASE Databases (restricted to clinically sound studies)		
	From launch to terminal curve date (year ending 2007)	3 years before launch	3 years post-launch
Sildenafil	160	2	33
Tadalafil	59	9	33
Vardenafil	43	5	29

Outcome measures

Most studies used specific elements of the International Index of Erectile Function (IIEF) questionnaire as a primary outcome, predominantly change from baseline scores to Q1-5 and 15 of the Erectile Function domain (Rosen *et al*., 1997). Some use the entire IIEF, while early studies often used just Q3 and Q4 that specifically addressed the key aspects of ED as defined by the NIH. Other primary and sometimes secondary outcomes were responses to Q2 and Q3 of the Sexual Encounter Profile (SEP) and a Global Assessment Question (GAQ) highlighted below:

IIEF *Q3: When you attempted sexual intercourse, how often were you able to penetrate your partner?*

Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated your partner?

SEP *Q2: Were you able to penetrate your partner (intercourse attempt)?*

Q3: Did your erection last long enough for you to complete intercourse?

GAQ*: Has the treatment you have been taking improved your erections?*

IIEF questions utilise a 1-5 grading scale to quantify the magnitude of response, but responses are subjective, as is data from the GAQ, and therefore the most relevant measure in an ED study is whether the drug has enabled the patient to complete intercourse successfully (SEP Q3).

9. Policy

The diffusion of the PDE5 inhibitors has been considerably impacted upon by government policy. Sildenafil presented an unprecedented challenge for policy makers, forcing acknowledgement of the need for rationing in the NHS. Following fears that excessive demand and inappropriate recreational use could cost the health service more than £1 billion a year, the then Secretary of State for Health issued interim guidance through a Health Service Circular (HSC) the day before sildenafil was licensed in Europe, advising that doctors should not prescribe the drug until further notice. The temporary moratorium on sildenafil was intended as a holding position while the Department of Health considered its longer-term view, with a decision on the final status anticipated at the end of that year after seeking further expert advice. In the interim, GPs could issue prescriptions privately, but not to their own patients or those of their practice partners.

On 21st January 1999, draft guidelines were issued following public consultation, placing drug treatment of ED into Schedule 11 of the 1992 General Medical Services Regulations (subsequently became Schedule 2), which lists drugs, medicines and other substances that qualify for prescription at NHS expense only in certain circumstances. It included six conditions and two qualifier groups that would be eligible to receive sildenafil on the NHS. While acknowledging ED could cause psychological distress, the Government's position was that ED was not life-threatening, or causes physical pain. The intention of the guidelines was to limit the cost of the drug to around £10-12 million per year (Department of Health, 1999c) and distinguish between patients with real physical need from those who wanted to improve performance, a misconception that persisted despite Pfizer emphasising sildenafil was not a performance enhancer in a normal healthy male (Brooks, 1998).

The increased role of specialists in the DH proposals to determine 'severe distress' was met with mixed opinions from both primary and secondary care. GPs felt that their position was being undervalued and that it was inappropriate for specialists to assess distress when they were often in a better position to do so. Equally, urologists did not want prescribing confined to specialists for fear of overburdening their already stretched outpatient clinics and ultimately restricting access to what they believed was a genuine innovation (Berger, 1998). Other GPs however, were not as keen on it becoming a primary care concern due to difficulties in making a true diagnosis of ED, coupled with the cost implications to fixed prescribing budgets.

In May 1999, following public pressure six further conditions were added to the exceptions to prescribing. Additionally, the frequency of treatment was recommended as one treatment per week, as due to the 'street value', excessive prescribing could lead

to unlicensed use of the drug (Department of Health 1999d). In a change to the initial situation, anyone not eligible, could receive a private prescription from their own GP, and not be charged for the consultation. The changes came into effect on 1st July 1999 and were intended to provide a balance between treating men with impotence whilst protecting NHS resources for other priorities. This landmark decision was not based on clinical effectiveness grounds, and so was considered conclusive proof of the first acknowledgement of rationing in the NHS, whilst also raising the issue of priority given to the treatment of a 'lifestyle' condition such as ED under the NHS in contrast to life threatening conditions.

Other policy challenges

There still remains little or no central funding allocated to ED (Wright, 2006), but in November 2007, recommendations were submitted that routine enquiries about erectile function should be included as specific indicators in the diabetes and cardiovascular disease domains of the QOF, and in doing so help to reduce GPs reluctance to broach the subject. As a condition that affects the vasculature, ED is considered an early marker of underlying chronic illness, notably atherosclerosis and diabetes (Thompson *et al*., 2005). In 2011, pilots using indicators developed from NICE guidelines to incentivise practices to case-find and prescribe treatment for ED in men with diabetes were ongoing before consideration for inclusion in the 2013/2014 QOF review (NICE, 2010).

Earlier proposals to include non-diabetic cardiovascular disorders within the conditions permitted under Schedule 11 were rejected on the basis it would increase NHS eligibility beyond what could be sustained.

10. Guidelines

There have been numerous national and international guidelines published on the management of ED. While NICE has not produced guidance specifically on the management of ED, the condition has been recognised within its diabetes guidelines (see PDE5 inhibitor timeline commentary). Following the launch of sildenafil, all guidelines reflected the same message of the importance of the use of oral PDE5 inhibitors as first-line therapy. There was also significant activity to update recommendations following the launch of tadalafil and vardenafil, although insufficient evidence was available to advise the use of one PDE5 inhibitor above any other. Therefore the impact of guidelines was likely to have been limited. Inclusion of ED within the NICE diabetes clinical guidelines provided an opportunity to assess and educate men on the organic causes of ED, and be offered treatment with a PDE5 inhibitor when they may have otherwise been reticent to seek help for the condition (NICE, 2004a).

11. Cost

In retrospect, the cost projections were excessively high which reflected the uncertainty about the prevalence of the condition. The BMA's projections were £1.25 billion a year if all men who could benefit were prescribed the drugs, which was a quarter of the total

drugs budget for the NHS. NHS projections were around £100 million, while Pfizer's projections were that the market would stabilise at around £50 million a year after 5 years (Brooks, 1998). The restrictions were a necessary means of keeping spending in line with the modest priority for NHS funding afforded to this condition. Despite these measures, by 2001 NHS expenditure for impotence was double that initially intended at around £25 million a year (Department of Health, 2001).

The NHS price of all three PDE5 inhibitors for the recommended starting dose was £4.86 per tablet (private cost: £12 each), which compared to sublingual apomorphine (£5.34 per tablet) and intraurethral aloprostadil with its associated side effects (Caverject £6.74 per dose), are both clinically and cost effective. A cost-utility analysis conducted by Stolk and colleagues (2000), demonstrated that sildenafil was cost effective compared with conventional treatment[46] with an incremental cost effectiveness ratio in the first year of £3,639. However, in the absence of a substantial transfer in responsibility for the management of ED to primary care due to Schedule 11 restrictions, the potential cost effectiveness benefits of PDE5 inhibitors were not fully realised.

12. Marketing

Despite restrictions on direct to consumer advertising in the UK, a unique level of patient awareness of sildenafil resulted from an unprecedented media interest in this subject in the months intervening between its US and UK launches. The unanticipated response of the Government to the drug also ensured the topic remained in the headlines for several months after. Pfizer's main challenge was to move the discussion away from a sexual context, which the media were keen to perpetuate, towards a medical issue to help men overcome the embarrassment that accompanies the condition. Their marketing approach, sometimes described as 'aggressive' by commentators, focussed heavily on the physical aspects of the condition (Neumeyer and Kirkpatrick, 2004). Their campaigns tended to feature just men, often using sports stars to convey a concept of performance, or famous spokesmen with the condition capable of empathising with patients.

With its differing pharmacokinetic profile, Lilly was able to take a more couples focussed approach by offering renewed intimacy from tadalafil. Bayer initially followed a similar approach to Pfizer, but they later pursued the relationship angle and difficult to treat subpopulations with vardenafil (Neumeyer and Kirkpatrick, 2004). Sectioning patients into niche groups by subgroup based on the cause of ED, or according to time of onset of action, was crucial for the other two companies involved as it made the market more accessible when confronted with such a powerful brand as Viagra. It reduced competition and enabled advertising campaigns to be tailored to the needs of the individual groups.

[46] Conventional treatment included papaverine/phentolamine injections which were not licensed in the UK for erectile dysfunction.

Appendix 16: Background literature on the statins for the prevention of first and recurrent cardiovascular events through lipid lowering

1. Cardiovascular disease (CVD)

In addition to cholesterol, there are many other factors that influence a person's risk of developing coronary heart disease (CHD), including age, sex, ethnicity, a family history of premature heart attack or heart disease indicating a genetic predisposition, socio-economic status, smoking, obesity, hypertension and type 1 and 2 diabetes mellitus (NICE, 2006). The risk of a future cardiovascular event can be calculated from these risk factors and people at highest risk can be identified.

As cholesterol levels are a modifiable risk factor, cholesterol management i.e. reducing overall total cholesterol (TC) by reducing low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) and increasing high-density lipoprotein cholesterol (HDL-C) sometimes referred to as 'good' cholesterol either through diet, exercise and/or drugs, is a key strategy in reducing morbidity and mortality from CVD. Around 20% of cholesterol in the body comes directly from food, but the remaining 80% is synthesised endogenously in the liver by an enzyme called HMG-CoA reductase, the target of the statins.

2. Diagnosis

The magnitude of statin derived benefit is related to the individual's baseline risk of CHD events and to the degree of cholesterol lowering, but not to the initial cholesterol concentration. The decision to initiate statin therapy therefore is not based on lipid levels alone (fasting TC, LDL-C, HDL-C and TG), but takes into account an individual's overall CVD risk assessment (Gotto and LaRosa, 2005).

In primary CVD prevention, patients with one or more risk factors can benefit from statins even if they do not have substantially elevated cholesterol levels. An appropriate risk calculator designed to estimate a person's 10 year cardiovascular event risk is used as an aid to making clinical decisions about how intensively to intervene with lifestyle measures and drug treatments (NICE, 2006). Before a statin is offered in primary prevention, all other modifiable risk factors should be managed. This is opposed to secondary prevention where lipid therapy is initiated immediately.

3. Prognosis

CHD was responsible for 160,000 deaths in the UK in the 1960's. This figure has now more than halved, a reduction of which a significant proportion has been due to the use of statins (British Heart Foundation, 2011). The effect of statin therapy is rapid, with results evident within one week and maximal lipid lowering effect achieved after four to six weeks. A review of long-term primary and secondary prevention trials by the

Cholesterol Treatment Trialists found that for every mmol/L reduction in LDL-C, there is an overall 12% reduction in all-cause mortality; largely reflecting significant reductions in deaths due to CHD and other cardiac causes (Baigent *et al*., 2005)

Compliance

After 3-4 years of treatment, continuation rates in secondary and primary prevention trials remained high at 75% and 87%, respectively (NICE, 2006). However, after 10 years only around 40% of patients are still taking statins (Benner *et al*., 2002), which although is characteristic of chronic asymptomatic conditions, may also be attributable to adverse effects.

4. Setting of care

While secondary care influences statin prescribing practice, these drugs are predominantly prescribed within primary care, accounting for approximately a million prescriptions a week in the UK (Trusler, 2011). Most patients are managed within primary care specialist lipid, diabetic or cardiac clinics often run by practice nurses who are also responsible for setting up monitoring systems to identify new patients at high risk of CHD. These types of initiatives are often supported by statin manufacturers, such as Pfizer's CHD Cascade programme that provided training in improving CHD management.

5. Pharmacological mechanism

Statins block the endogenous synthesis of cholesterol in the liver by selectively inhibiting the enzyme HMG-CoA reductase. A reduction in intracellular cholesterol has a secondary effect of stimulating the production of LDL receptors on the surface of liver cells, which increase the removal of circulating LDL-C from the blood. Statins have also been shown to raise HDL-C levels and reduce triglycerides, although to a lesser extent than fibrates.

Statins are divided into two groups; the early statins such as simvastatin and pravastatin are fermentation-derived, while atorvastatin and rosuvastatin are synthetically produced. They are differentiated predominantly according to their potency profiles, cerevastatin being the most potent, followed by rosuvastatin, atorvastatin, simvastatin, pravastatin and fluvastatin.

In addition to their cholesterol lowering ability, several other mechanisms have been proposed to explain the beneficial effects of statins. The improvement in reducing stroke seen with statins, but not with other LDL-C lowering drugs such as fibrates, indicates that statins may stabilise plaques. Stabilisation of coronary lesions is most likely the main reason for survival, but improvement of endothelial function, prevention of thrombus formation and modulation of inflammatory responses are also potential mechanisms.

6. Licensed indications

The impact of statins in reducing cardiovascular events and mortality is predominantly due to their LDL-C lowering efficacy, but as they also increase HDL-C and reduce levels of TGs to varying degrees, their licensed indications reflect multiple types of lipid disorders (NICE, 2006).

Table A16.1: Licenced indications of statins

Indication	Licensed as an adjunct to diet in people with:	Simvastatin	Atorvastatin	Rosuvastatin
Primary hypercholesterolaemia	High cholesterol levels in the blood due to an underlying genetic cause (indication can be inclusive of heterozygous familial hypercholesterolaemia).	✓	✓	✓
Homozygous familial hypercholesterolaemia	Rare genetic disorder causing extreme elevations of LDL-C due to defective LDL receptor genes. Leads to premature CHD in the absence of any other risk factor or coronary disease.	✓	✓	✓
Heterozygous familial hypercholesterolaemia	Only one of the pair of LDL receptor genes is defective or mutated.	-	✓	-
Mixed hyperlipidaemia	Increase in lipids (TC; LDL-C, TG). Does not include reduced HDL-C. Often associated with metabolic syndrome, non-alcoholic fatty liver disease, and risk of developing type 2 diabetes.	-	✓	-
Mixed dyslipidaemia	Abnormal levels of more than one lipid fraction (elevated TC, LDL-C or triglycerides, or low HDL-C).	✓	-	✓
Reduction of CVD mortality/morbidity	General indication in people with atherosclerotic CVD or diabetes mellitus (with normal or increased cholesterol levels).	✓	-	-
Starting doses		20mg (40mg if >45% LDL-C reduction)	10-20mg (40mg if >45% LDL-C reduction)	10mg (20mg if LDL-C >4.87mmol/L).

<u>Atorvastatin</u>

The development of atorvastatin was nearly abandoned by Warner-Lambert in the early stages on the premise that it was bringing nothing new to an already crowded market. However, a trial in 24 employee-volunteers found that at its lowest dose (10mg) it was more effective than simvastatin at its highest, causing a 38% reduction in LDL-C. A lack of pipeline development, combined with the potentially huge statin market meant that even with a 10% market share, it would become Warner-Lambert's biggest selling drug convincing them to continue with development, which they co-marketed with Pfizer.

As a later entrant to the statin market, Pfizer and Warner-Lambert were able to leverage the efforts of other companies to raise consumer awareness and clinicians' confidence in the use of statins. They were however, at a disadvantage at launch in that they could only present surrogate data for atorvastatin compared with the clinically relevant endpoint data of its competitors, but the 4S study had strengthened support for the LDL-

C reduction argument. Their strategy was to invest in a substantial clinical trial programme that reported over the next six years, firstly to evaluate statin use in specific subpopulations, and secondly to determine the impact of atorvastatin's enhanced potency on clinical outcomes. In doing so, they addressed some of the concerns raised by previous studies, with one of Pfizer's key marketing messages being 'lower is better'.

Rosuvastatin

AstraZeneca believed there was a compelling medical need for another statin in what was already a crowded market, as millions of people were still at risk of CVD, either through remaining untreated or not being effectively treated with other lipid lowering therapies (McKillop, 2003). Differentiation was based on its ease of use, as more than 80% of patients reached their LDL-C goals on the starting dose of 10mg, and unlike other statins it also significantly increased HDL-C (atorvastatin demonstrated a negative dose response curve in relation to HDL-C, with higher doses becoming progressively worse). The 40mg dose was reserved for people with severe hypercholesterolaemia at high cardiovascular risk and required specialist supervision and routine follow up. Rosuvastatin's greater potency enabled 17% of patients with familial hypercholesterolaemia to reach acceptable levels at a dose of 40mg compared with 4.5% with atorvastatin 80mg (Stein *et al*., 2003).

The development programme was the largest and most comprehensive in the statin class containing four times the number of patients of that for any other previously approved statin. More than 63,000 patients were recruited worldwide to participate in the Galaxy trial portfolio (consortium of 16 clinical trials), a strategy which enabled clinicians to become familiar with the new statin ahead of launch, and so contributed to raising confidence. AstraZeneca also invested heavily in the marketing campaign (reported cost of around $1 billion), featuring an unprecedented sampling programme of 500,000 30 day samples (most used 7 day supplies) to raise awareness and encourage clinicians to try the drug.

As with all other statins, at launch rosuvastatin could only compete on surrogate evidence (LDL-C lowering efficacy or atherolsclerosis progression) in a market that was now heavily dominated by clinical endpoint data. A Lancet editorial in 2003 urged clinicians to inform patients that compared with its competitors, rosuvastatin had an inferior evidence base (Horton, 2003). While this was true in terms of clinical endpoints and long-term safety data (the first study to evaluate the impact of rosuvastatin on mortality and morbidity outcomes (CORONA) was not published until late 2007 (Kjekshus *et al*., 2007)), AstraZeneca responded by highlighting this was the case for any new drug entering a market, and that safety had been rigorously assessed by regulatory authorities. At this late stage in the diffusion of statins, the class safety profile and the correlation between lipid lowering and clinical benefit were well established, such that surrogate endpoints were widely accepted in clinical decision making (McKillop, 2003).

7. Safety and regulation

Statins are the most extensively studied drugs available and while being considered relatively safe at moderate doses, some have been affected by serious safety issues at high doses. Common adverse reactions of statins include myalgia (muscle pain), mild transient gastrointestinal symptoms (diarrhoea, constipation), elevated hepatic transaminases, headache, insomnia, joint pain and/or dizziness. Serious adverse events including myopathy (muscle weakness) and rhabdomyolysis (an extreme form of myopathy causing the breakdown of skeletal muscle proteins into the blood, potentially leading to acute renal failure), are relatively rare (1 in 1,000 and 1 in 10,000, respectively) (Jacobson, 2006). While this appeared to be the case in randomised controlled trials, in observational studies and clinical experience rates were higher, which reduced confidence in lipid lowering therapy contributing to its underuse (Fernandez, 2011). Cerevastatin was withdrawn, and rosuvastatin was adversely affected by rhabdomyolysis safety issues.

Generic simvastatin

With the eventual reduction in price of generic simvastatin, it replaced the lower doses of atorvastatin, which accounts for the vast majority of prescriptions. Over time, statin doses had been increasing and targets had become more aggressive, limiting the impact that generic simvastatin could achieve, but there is a threshold where lipid lowering effect reaches a plateau and side effects increase. However, people who fail to reach target, or have very high initial base-line levels, or progressive disease despite lipid lowering therapy, or following recent acute coronary syndrome require more intensive lipid lowering therapy to reduce LDL-C by around 55%. This can be achieved through atorvastatin and rosuvastatin monotherapy, or with the addition of ezetimibe (Zetia) to simvastatin 40mg (the additional cost of ezetimibe however, made this combination more expensive than monotherapy, even after the significant price drop of generic simvastatin). High dose simvastatin (80mg) has been associated with higher rates of myopathy than high dose atorvastatin and is therefore not generally recommended for this degree of lipid lowering (de Lemos *et al*., 2004; Nissen, 2004).

8. Efficacy

Marketed statins lower TC by 13-46%, LDL-C by 17-61%, triglycerides by 7-37% and raise HDL-C by 5-15%. In the major primary and secondary prevention studies, the percentage change in TC ranged from 18-25%[47]. A meta-analysis of these studies (NICE, 2006) indicates that therapy with a statin (providing a mean reduction in TC of 20%) is associated with the clinical benefits as detailed in Table A16.2.

[47]The ALLHAT-LLT pravastatin study produced only a 10% reduction in TC (the small reduction was attributed to many in the placebo arm also receiving lipid lowering drugs by the end of the study). The non-significant cholesterol difference potentially accounted for the null study result.

Table A16.2: Clinical impact of statin therapy (NICE, 2006)

	Relative Risk Reduction[48]			
	All (primary and secondary)	Secondary	Primary (without CVD)	Primary (without CHD)
Fatal outcomes				
All cause mortality	17%	21%	ns	17%
Cardiovascular mortality	21%	25%	ns	ns
CHD mortality	23%	28%	ns	ns
Fatal MI	46%	43%	59%	59%
Stroke	ns	ns	ns	ns
Non-fatal outcomes				
Stroke	25%	25%	ns	ns
MI	32%	31%	40%	42%
Unstable angina	12%	18%	ns	ns
Revascularisation	25%	23%	ns	ns

ns= non significant

At the time of the NICE technology appraisal on statins, there was no data on clinical events to suggest the superiority of any one statin over all the others in reducing cardiovascular events.

8.1. Statin Trials

The key trials relevant to the case study drugs are outlined in the statin timeline. However, throughout the late 1990s and early 2000s a whole series of large scale clinical trials were conducted that confirmed the cardiovascular benefits of the statin class in:

- **Secondary prevention**: 4S; CARE; LIPID; HPS; GREACE[49]; LIPS[50];
  - *Intensive lipid lowering (Stable CHD):* TNT[51]; IDEAL; AVERT; ALLIANCE
  - *Intensive lipid lowering (acute coronary syndrome):* PROVE-IT TIMI 22; MIRACL[52]; A to Z[53]
- **Primary prevention**: WOSCOPS; AFCAPS/TEXCAPS[54]; ASCOT-LLA; CARDS[55]; ASPEN[56]; 4D[57]; HPS (contained people with and without CHD)

[48] While the relative risk reductions (RRRs) appear substantial, the absolute risk reductions (ARRs) are conservative (e.g. all cause mortality in 4S study: placebo 11.2% vs simvastatin 8.2%: RRR=30%, ARR=3.3%; CHD mortality in LIPID study: placebo 8.3% vs pravastatin 6.4%: RRR 24%, ARR 1.9%).
[49] **GREACE:** GREek Atorvastatin and Coronary heart disease Evaluation (Athyros *et al.*, 2002)
[50] **LIPS**: Lescol Intervention Prevention Study (Serruys *et al.*, 2002) - fluvastatin
[51] **TNT**: Treating to New Targets (LaRosa *et al*., 2005) - atorvastatin
[52] **MIRACL**: Myocardial Ischaemia Reduction with Aggressive Cholesterol Lowering (Schwartz *et al*., 2001) – atorvastatin
[53] **A to Z**: Phase Z of the Aggrastat to Zocor study (de Lemos *et al.*, 2004) – simvastatin
[54] **AFCAPS/TexCAPS**: Air Force/Texas Coronary Atherosclerosis Prevention Study (Downs *et al.*, 1998) - lovastatin
[55] **CARDS**: Collaborative AtoRvastatin Diabetes Study (Colhoun *et al*., 2004)
[56] **ASPEN**: Atorvastatin Study for Prevention of coronary heart disease Endpoints in Non-insulin-dependent diabetes mellitus (Knopp *et al*., 2006) - atorvastatin
[57] **4D**: Deutsche Diabetes Dialyse studie (Wanner *et al*., 2005) - atorvastatin

- **Across a wide age range:** CARE; HPS; LIPID; ALLIANCE; PROSPER[58]; ASCOT-LLA
- **People with lower than average total cholesterol levels**: CARE; HPS; LIPID
- **Diabetes**: HPS**;** CARDS; ASPEN; 4D
- **Hypertension:** ALLHAT; ASCOT-LLA
- **Stroke:** SPARCL

The footnoted studies were not included in the timeline on the basis of subpopulation analysis or earlier studies addressing the same or similar concepts. The most influential statin trial was the 4S study published in 1994 (Scandinavian Simvastatin Survival Study Group, 1994), which was the first to demonstrate the link between lowering LDL-C and reducing overall mortality in an era when evidence-based medicine was increasing in importance.

By the time atorvastatin entered the market in 1997, there had been a shift in attitude towards the statins. At launch, the surrogate endpoint study CURVES (Jones *et al*., 1998) was able to demonstrate atorvastatin's greater LDL-C lowering efficacy, but clinical endpoint data did not emerge until around two years later from the AVERT trial (Pitt *et al*., 1999), and it was not until 2003 that the first trial demonstrating a reduction in cardiovascular mortality (ASCOT-LLA) was published (Sever *et al*., 2003). Atorvastatin was competing with statins with proven clinical endpoints, but this did not affect its uptake. The fact that within approximately two years of launch, atorvastatin had reached an adoption rate on a par with simvastatin, which had been on the market for 10 years, could support the argument for aggressive marketing as opposed to evidence-based medicine (Walley *et al*., 2005), but confidence in the statin effect was such that extrapolations were being made on the basis of atorvastatin's greater lipid lowering efficacy. While the Heart Protection Study (Heart Protection Study Collaborative Group, 2002) provided a strong argument for using simvastatin, atorvastatin did benefit from an overall boost in statin use as the price differential between them at that time was small.

Pravastatin's diffusion was negatively impacted upon by the ALLHAT-LLT trial (ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002) and fluvastatin was not widely prescribed in the UK as it was expensive for the extent of lipid lowering obtained (even at maximal dose it was less effective than either simvastatin 40mg or atorvastatin 10 and 20mg). This left the statin market dominated by simvastatin and atorvastatin. Rosuvastatin launched with the surrogate endpoint STELLAR trial (Jones *et al*., 2003), demonstrating its superiority in terms of lipid lowering efficacy and raising HDL-C, even at very low doses, but clinical endpoint studies were not published in the remaining period covered by the diffusion curve.

[58] **PROSPER**: PROspective Study of Pravastatin in the Elderly at Risk (Shepherd *et al*., 2002)

8.2. Intensive lipid lowering

The 'fire and forget' approach to lipid lowering proposed in 2002 (Shepherd, 2002), involved prescribing a standard dose of statins without further testing or dose adjustment. However, the prospect of greater potency altered the focus of trials towards more aggressive lipid lowering and an alternative approach of 'treating to target', which aims to achieve target concentration of LDL-C through titration. The argument for intensive lowering has been controversial as the vast majority of people do not need to reduce their cholesterol levels to this degree. Studies such as CARE (Sacks *et al*., 1996) had suggested that there might be a LDL-C threshold of around 3·2mmol/L, however the Heart Protection Study (Heart Protection Study Collaborative Group, 2002) and PROVE IT-TIMI 22 trial (Cannon *et al*., 2004) demonstrated that lowering LDL-C from below 3mmol/L to below 2mmol/L reduced vascular disease risk by about one quarter, which is similar to the proportional reduction in risk produced by a 1mmol/L reduction at higher LDL-C concentrations. Several other intensive lipid lowering trials (TNT [LaRosa *et al*., 2005]; ALLIANCE [Koren *et al*., 2004]; A to Z [de Lemos *et al*., 2004]) have demonstrated the ability to improve morbidity, but not mortality. The concern underpinning the intensive lipid lowering argument was that the more conservative guidelines may inadvertently lead to substantial under-treatment of high-risk patients who present with LDL-C concentrations below, or close to, particular targets (Heart Protection Study Collaborative Group, 2002).

Table A16.3 summarises the extent of the research activity in statins compared to the other case studies from launch up until 2007 and for the initial periods pre- and post-launch. In a crowded market, evidence generation appears to be particularly important in substantiating claims of differentiation, as demonstrated by similar numbers of studies generated by all three drugs, despite entering the market at different positions.

Table A16.3: Statins: volume of evidence: MEDLINE and EmBASE searches

Statins	**No. of studies included on MEDLINE/EmBASE Databases (restricted to clinically sound studies)**		
	From launch to terminal curve date (year ending 2007)	3 years before launch	3 years post-launch
Simvastatin	197	2	19
Atorvastatin	165	3	21
Rosuvastatin	37	4	24

9. Guidelines

Cholesterol targets: 5 and 3mmol/L

Guidelines, by setting and changing the cholesterol targets, are influential in determining the eligible patient population for statins. In the early 1990s, optimal cholesterol goals in Europe and the USA were set at either 5mmol/L for TC and 3mmol/L for LDL-C, or a 25% reduction in TC and a 30% reduction in LDL-C, whichever achieved the lowest absolute value: Joint British Societies guidelines JBS1 (Wood *et al.*, 1998a); Joint European Societies guidelines JES 1 (Pyorala *et al*., 1994) and JES 2 (Wood *et al*., 1998b); and the USA National Cholesterol Education

Programme – Adult Treatment Panel guidelines NCEP-ATP I (National Cholesterol Education Programme, 1988). Moderate statin therapy (40mg simvastatin) achieved these targets, but at a significant cost to the NHS (£1 billion) (Wierzbicki, 2007). Following the genericisation of simvastatin, there were significant efforts to promote the use of generic statins as their cost differential allowed 5-6 patients to be treated for each one on a patented brand.

Cholesterol targets: 4 and 2

In light of the evidence from trials investigating the impact of intensive lipid lowering, a lack of consensus developed between guideline recommendations and policy. The updated UK JBS2 guidelines (British Cardiac Society *et al*., 2005), European JES 3 guidelines (de Backer *et al*., 2003) and the American NCEP-ATP III guidelines (National Cholesterol Education Programme 2001) supported lowering targets to 4 and 2mmol/L, with a minimum standard of 5 and 3mmol/L.

The effect of driving down the medical consensus on the targets for cholesterol lowering was two-fold; it increased the number of patients eligible for statin therapy, and required more potent statins to achieve the lower targets. While simvastatin was available in 80mg doses, atorvastatin and rosuvastatin could achieve the same effect at much lower doses and therefore at reduced toxicity. The Department of Health however, kept targets at 5 and 3mmol/L in relation to the QOF indicators until NICE guidelines produced in May 2008 (just outside the time frame of the timeline) updated their recommendations to reflect the 4 and 2mmol/L targets for secondary prevention (NICE, 2008b).

Primary prevention risk estimates

In primary prevention, the JBS1 guidelines (Wood *et al*., 1998a) had recommended that individuals whose total CHD risk was ≥15% over 10 years were eligible for therapeutic intervention. While the NSF adopted a stance consistent with the JBS1 guidelines on cholesterol targets, for pragmatic reasons it set the risk level at ≥30%. However, in recognition of the gathering evidence base for lipid lowering, in the NICE statin technology appraisal in 2006, the risk level reduced to ≥20% (NICE, 2006).

NICE Appraisal: Statins

The NICE technology appraisal on statins (2006), produced at a relatively late stage in the diffusion of statins, recommended the use of statins in the secondary prevention of CVD and as part of the management strategy for primary prevention, advocating use of the statin with the lowest acquisition cost taking into account required daily dose and product price per dose. While this guidance favoured generic simvastatin or pravastatin at moderate doses, at higher doses, uncertainty related to the safety of 80mg simvastatin enabled the more potent statins atorvastatin and rosuvastatin to remain competitive in niche patient groups. Rosuvastatin was potentially disadvantaged as it could only make extrapolations of lipid profile data and not clinical endpoints as they were unavailable.

Related NICE guidance

A series of related NICE guidelines and appraisals were produced on diabetes, hypertension and myocardial infarction that discussed the context in which statins were recommended or appropriate lipid targets in these specific patient groups (see statin timeline commentary for details).

10. Policy

In the UK, the cholesterol targets of 5mmol/L and 3mmol/L were incorporated into policy, both in the National Service Framework for Coronary Heart Disease (NSF-CHD) (Department of Health, 2000) and in the Quality and Outcomes Framework (QOF) of the General Medical Services contract in 2004, which led to more than two thirds of patients with atherosclerosis requiring statin therapy (Wierzbicki, 2007). The standards set out in the NSF-CHD were intended to help achieve the ultimate target as set out in the Government white paper 'Saving Lives; Our Healthier Nation' (Department of Health, 1999a) of reducing the death rate from CHD, stroke and related diseases amongst people under 75 years by at least two-fifths by 2010 to save a total of 200,000 lives.

11. Cost

Instead of setting a premium for improved LDL-C lowering efficacy, the strategy of Warner-Lambert and Pfizer was to price atorvastatin lower than simvastatin. At an equivalent dose, a 28 day supply of atorvastatin cost £30.60 (20mg) versus £47.04 for simvastatin (40mg) (Joint Formulary Committee, 1997), enabling it to challenge simvastatin's dominance of market share. When rosuvastatin was launched, its increased potency meant that it was less expensive than its competitors at equivalent efficacy doses.

<u>Category M – generic prescribing</u>
Despite generic simvastatin entering the market in May 2003, it was not until April 2005 that the price of simvastatin fell dramatically following the introduction of Category M into the Drug Tariff when the new community pharmacy contract was launched. This category, intended for generic medicines, enabled the Government to set a single tariff price to reflect the average manufacturers' market price after discount, rather than the system that had existed before based on prices before discount, which had in the two years previously maintained a high cost for generic simvastatin. Table A16.4 shows the mean TC and LDL-C lowering efficacy of the available doses of marketed statins and their corresponding 28 day cost.

Table A16.4: Total cholesterol and LDL-cholesterol lowering efficacy of statins and 28 day pre- and post-generic costs (adapted from NHS Prescribing and Dispensing News, 2002).

Statins	**Mean TC reduction**	**Mean LDL-C reduction**	**28 day cost (£)**		
			2003 (post-generic)[59]		2005 (post-schedule M)[60]
			Branded	Generic	Generic
Simvastatin					
10mg	21%	28%	18.03	18.02	2.12
20mg	26%	35%	29.69	29.68	2.26
40mg	30%	41%	29.69	29.68	4.87
80mg	37%	48%	29.69	29.68	26.79
Atorvastatin					
10mg	28%	38%	18.03	-	-
20mg	35%	46%	29.69		
40mg	40%	51%	29.69		
80mg	46%	61%	29.69		
Pravastatin					
10mg	13%	19%	16.18	-	3.42
20mg	18%	24%	29.69		5.89
40mg	24%	34%	29.69		6.55
Fluvastatin					
20mg	13%	17%	12.72	-	-
40mg	19%	23%	12.72		
80mg	25%	34%	16.00		
Rosuvastatin					
5mg	30%	38%	-	-	-
10mg	33%	46%	18.03		
20mg	38%	52%	29.69		
40mg	40%	55%	29.69		

From a primary prevention perspective, statin use was initially controversial despite only requiring low doses due to cost effectiveness issues when scaled up on a population level. However, generic availability has enabled this to become a viable public health proposition.

[59]Joint Formulary Committee, British National Formulary (No 46) September 2003
[60]Joint Formulary Committee, British National Formulary (No 50) September 2005

Appendix 17: Participant company profiles

Note: Figures quoted reflect the time period during which the interviews took place.

1. AstraZeneca

AstraZeneca formed in April 1999 through the merger of Astra AB of Sweden and Zeneca Group plc, UK. The company is engaged in research, development, manufacturing and marketing of prescription pharmaceuticals, with a main research focus in the following five therapeutic areas: cancer, cardiovascular, gastrointestinal, infection, neuroscience, respiratory and inflammation. In 2007, AstraZeneca was fourth in the list of the top 10 leading pharmaceutical corporations in the UK, with UK total market sales of £668 million.

Quetiapine
Quetiapine (Seroquel) accounted for sales of £92 million, which positioned it as AstraZeneca's second best selling product in the UK, as well as in its worldwide portfolio, and 12th in the list of the top selling pharmaceutical products in the UK (ABPI, 2010). Quetiapine's patent expired in 2012.

Rosuvastatin
Rosuvastatin (Crestor) was originally developed by Shinogi who granted AstraZeneca an exclusive worldwide licence in April 1998. In 2007, rosuvastatin sales accounted for £61 million, positioning it as AstraZeneca's fourth best selling product in the UK, and 30th in the list of the top selling pharmaceutical products in the UK (ABPI, 2010). Rosuvastatin's patent is due to expire in 2017.

2. Bayer Schering

Bayer AG is an international research based company founded in 1863 with headquarters based in Leverkusen, Germany. Its three business units include Healthcare; CropScience and MaterialScience, with Healthcare accounting for the largest proportion of sales (53%). Bayer Healthcare Pharmaceuticals is one of four divisions of Bayer Healthcare, comprising General Medicine; Haemology and Neurology; Diagnostics and Imaging; Oncology and Women's Healthcare. In 2006, Bayer acquired Schering Healthcare AG to become one of the world's leading pharmaceutical specialists.

In 2007, Bayer Schering was 14th in the list of the top leading pharmaceutical corporations in the UK, with total UK sales of £195 million (ABPI, 2010). In the year ending 2007, vardenafil was Bayer's eighth best selling product, accounting for worldwide sales of €332 million[61]. In the absence of direct UK sales figures for vardenafil, proportional sales in the UK based on worldwide sales, would have been in the region of £6.3 million for the same year. Vardenafil's patent is due to expire in 2018.

[61] Bayer Annual Report 2007

3. Janssen-Cilag

Janssen-Cilag (previously referred to as Janssen L.P.) is a division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. (a subsidiary of Johnson & Johnson). Janssen-Cilag focuses exclusively on mental health and markets prescription medications for the treatment of schizophrenia, bipolar mania, and irritability associated with autism. Janssen L.P. was founded in 1953 and is headquartered in Titusville, USA. In 2007, Janssen-Cilag, as a franchise of Johnson and Johnson, was 11th in the list of leading pharmaceutical corporations in the UK, with UK total market sales of £256 million.

In 2007, sales of risperidone (Risperdal) accounted for £56 million, positioning it as Janssen-Cilag's best selling product in the UK, and 38th in the list of top selling pharmaceutical products in the UK (ABPI, 2010). Risperidone's patent expired in 2008.

4. GSK

GlaxoSmithKline (GSK) is the second largest company in terms of sales in the UK after Pfizer. It is a UK headquartered company that was formed in 2000 through the merger of Glaxo Wellcome plc and SmithKline Beecham plc. Each of these companies had a long heritage in pharmaceutical research and development and were themselves formed through a series of mergers and acquisitions. GSK has a varied portfolio of products for major disease areas including asthma, mental health, diabetes, cardiovascular disease, digestive conditions, virus control, infections and cancer. In 2007, GSK was second in the list of the top 10 leading pharmaceutical corporations in the UK, with UK total market sales of £1.06 billion.

5. Lilly

Eli Lilly and Company was founded in May 1876. Now known as Lilly, their global headquarters are located in Indianapolis, USA. They are a research based company with a focus on five medical specialty areas: cardiovascular, endocrinology, neurology, oncology and rheumatology. Lilly have had significant experience of the mental health market with their selective serotonin reuptake inhibitor fluoxetine (Prozac), which like olanzapine was not a first in class drug but achieved blockbuster status within a short period post-launch. In 2007, Lilly was ninth in the list of the top 10 leading pharmaceutical corporations in the UK, with UK total market sales of £345 million.

<u>Olanzapine</u>
Olanzapine (Zyprexa) accounted for £162 million, which positioned it as Lilly's best selling product in the UK, and fourth in the list of the top selling pharmaceutical products in the UK (ABPI, 2010). Olanzapine's patent expired in 2011.

Tadalafil

In the year ending 2007, tadalafil was Lilly's fifth best selling product, accounting for worldwide sales of $1.2 billion[62]. In the absence of direct UK sales figures for tadalafil, proportional sales in the UK based on worldwide sales, would have been in the region of £22.5 million for the same year. Tadalafil's patent is due to expire in 2016.

6. Merck Sharp & Dohme (MSD)

Merck Sharp & Dohme Limited (MSD) is the UK subsidiary of Merck & Co in the USA. Sharp & Dohme established their partnership in the UK in 1906, and merged with Merck & Co Inc. in 1953 to create MSD. MSD are a research-based company and focus on treatments for atherosclerosis and cardiovascular disease, diabetes, infectious diseases, neuroscience and ophthalmology, respiratory, bone, arthritic conditions, and vaccines. In 2007, Merck & Co was eighth in the list of the top 10 leading pharmaceutical corporations in the UK, with total UK sales of £353 million (ABPI, 2010).

Alendronate

Alendronate (Fosamax) lost it patent in February 2008, but in the year ending 2007, it was Merck & Co's third best selling product, accounting for global sales of $3 billion[63]. In the absence of direct UK sales figures for alendronate, proportional sales in the UK based on those in the USA, would have been in the region of £44 million for the same year. Alendronate's patent expired in 2006.

Simvastatin

In 2007, simvastatin accounted for sales of £102 million, which positioned it as 10th in the list of top selling pharmaceutical products in the UK. In sales terms, this position reflects the impact of genericisation following the loss of MDS's patent in May 2003, putting simvastatin behind branded atorvastatin. However, the diffusion curve hierarchy reflects drug usage and therefore simvastatin maintained first position.

7. Procter & Gamble (P&G)

P&G are the world's largest fast moving consumer goods (FMCG) company. They market more than 300 consumer brands in 160 countries. The company operates through three global business units: Beauty and Grooming, Health and Well-Being, and Household Care. Before P&G sold its pharmaceutical division to Warner Chilcott in October 2009, the Health Care division that developed pharmaceuticals, oral and personal health care products, contributed 17.5% of total sales in 2008 (of which pharmaceuticals formed a significant proportion).

In 2007, P&G was 24th in the list of the top 10 leading pharmaceutical corporations in the UK, with total sales of £92 million.

[62] Lilly Annual Report 2007
[63] Merck & Co Annual Financial Report 2007 – product sales

Risedronate

Risedronate (Actonel) accounted for £48 million, which positioned it as P&G's best selling product in the UK in 2007, and 43rd in the list of top selling pharmaceutical products in the UK (ABPI, 2010). Risedronate's patent expired in 2010.

Etidronate

Etidronate's patent expired in March 1998 and so it has been available generically for many years, hence the requirement to plot diffusion curves on the basis of usage, as opposed to sales. It was not possible to identify sales figures, but it did not feature within the top 50 pharmaceutical products in the UK in 2007.

8. Pfizer

Pfizer Inc. was founded in New York in 1849 and is the world's largest research-based pharmaceutical company, with a focus on 11 therapeutic areas including oncology, cardiovascular, pain, neuroscience and infectious diseases. Pfizer Limited is the principal UK subsidiary of Pfizer Inc., comprising 4 divisions; Pharmaceutical Business (Established Products, Oncology, Primary Care and Specialty Care); Diversified Business (Nutrition, Consumer Healthcare and Animal Health); Research and Development; and Manufacturing and Distribution. Pfizer Inc. acquired Warner-Lambert in 2000 and in doing so, gained Parke-Davis branded pharmaceuticals including atorvastatin (Lipitor). In 2003, Pfizer acquired Pharmacia, making it the largest pharmaceutical corporation in the UK, with total UK sales of £1.1 billion in 2007. The company later merged with Wyeth in 2009.

Sildenafil

In 2007, sildenafil (Viagra) accounted for £62 million, which positioned it as Pfizer's third best selling product in the UK after atorvastatin (Lipitor) and pregabalin (Lyrica), and 26th in the list of top selling pharmaceutical products in the UK (ABPI, 2010). Sildenafil's patent expired in 2012.

Atorvastatin

In 2007, atorvastatin accounted for total UK sales of £456 million, positioning it as the top selling pharmaceutical product in the UK (ABPI, 2010). Once the price of generic simvastatin dropped significantly in 2005, atorvastatin's use declined, but in sales terms it still dominates. Atorvastatin's patent expired in 2012.

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