Deutsche Bank
Markets Research

Europe
United Kingdom
Pharmaceuticals
Pharmaceuticals

Industry
European Pharmaceuticals

Date
29 August 2012

Industry Update

Jeremy Lai, MD
Research Analyst
(+44) 20 754-58441
jeremy.lai@db.com

Tim Race, CFA
Research Analyst
(+44) 207 54-76522
tim.race@db.com

Mark Clark
Research Analyst
(+44) 20 754-75875
mark.clark@db.com

Richard Parkes, Ph.D
Research Analyst
(+44) 20 754-50470
richard.parkes@db.com

Holger Blum, DVFA
Research Analyst
(+41) 44 227-3376
holger.blum@db.com

Pharmaceuticals for Beginners 2012

Deutsche Bank
Markets Research

Europe
United Kingdom
Pharmaceuticals
Pharmaceuticals

Industry
European Pharmaceuticals

Date
29 August 2012

Industry Update

Pharmaceuticals for Beginners 2012

Jeremy Lai, MD
Research Analyst
(+44) 20 754-58441
jeremy.lai@db.com

Tim Race, CFA
Research Analyst
(+44) 207 54-76522
tim.race@db.com

Mark Clark
Research Analyst
(+44) 20 754-75875
mark.clark@db.com

Richard Parkes, Ph.D
Research Analyst
(+44) 20 754-50470
richard.parkes@db.com

Holger Blum, DVFA
Research Analyst
(+41) 44 227-3376
holger.blum@db.com

Welcome to the 2012 edition of Pharmaceuticals for Beginners

So, you've inherited the pharmaceutical sector. Big companies, large market capitalisations and interesting diseases with some funny-sounding names. Fantastic! You finally get to follow a sector that might actually be of interest to the person sitting next to you at a dinner party.

But wait. What is a GLP-1 analogue, and why can't analysts just say heart attack or heartburn instead of using lengthy terms like myocardial infarction or gastro-oesophageal reflux disorder? And what on earth is a randomised, placebo-controlled, double-blind, Phase III clinical trial anyway? Oh no, what have I gotten myself into?

In our view, the pharmaceutical industry is fascinating, exciting and of obvious relevance beyond the stock market. But it is also very technical and comprises a minefield of products, scientific terms and disease pathways. Keeping track of it all can at times prove bewildering, and not just for the uninitiated.

With this in mind, the pharmaceuticals team at Deutsche Bank first published a document in January 2001 that was targeted at beginners and industry veterans alike – "Pharmaceuticals for Beginners". The first and subsequent editions were such a success that we are now publishing our 2012 edition, which has been completely updated, while retaining much influence from the original.

This report is structured in two parts, with the first providing an introduction to the industry dynamics and regulatory framework governing pharmaceuticals, and the second containing an introduction to the different therapeutic markets. The current edition covers 32 disease areas, including new topics such as Pulmonary Arterial Hypertension and Epilepsy. We have also included overviews on topics such as emerging markets, vaccines, orphan genetic diseases, consumer health and animal health.

"Pharmaceuticals for Beginners" is not necessarily intended to be read cover to cover, but is meant as an easy-to-use reference guide. Although our intent was to provide professionals who are new to the pharmaceuticals sector with an introduction to a complex industry, we hope that our more learned readers will find new insights as well. Overall, we hope that this book will be a valuable resource that might find its own spot on many overcrowded desks.

Industry Overview

Therapeutic review

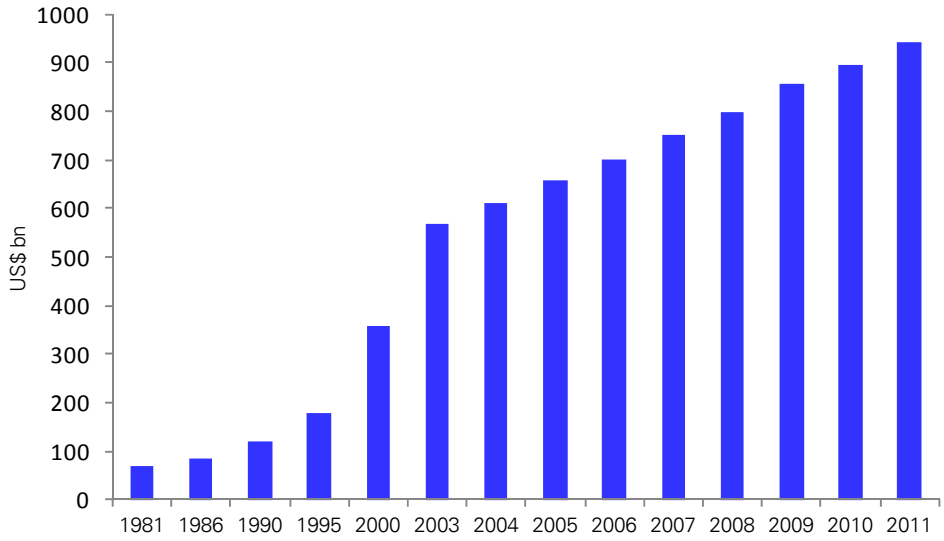
Therapeutic review (cont'd)

Introduction

A near $1 trillion industry

Global prescription drug revenues totalled $955 billion in 2011, compared with c.$70 billion in 1981, according to the industry consultancy IMS Health. The pharmaceuticals industry has thus recorded compound annual revenue growth of c.9% over this 30-year period, during which underlying volume growth has seen little sign of abatement.

Figure 1: Global pharmaceutical sales 1981-2011 ($ bn, constant currency)



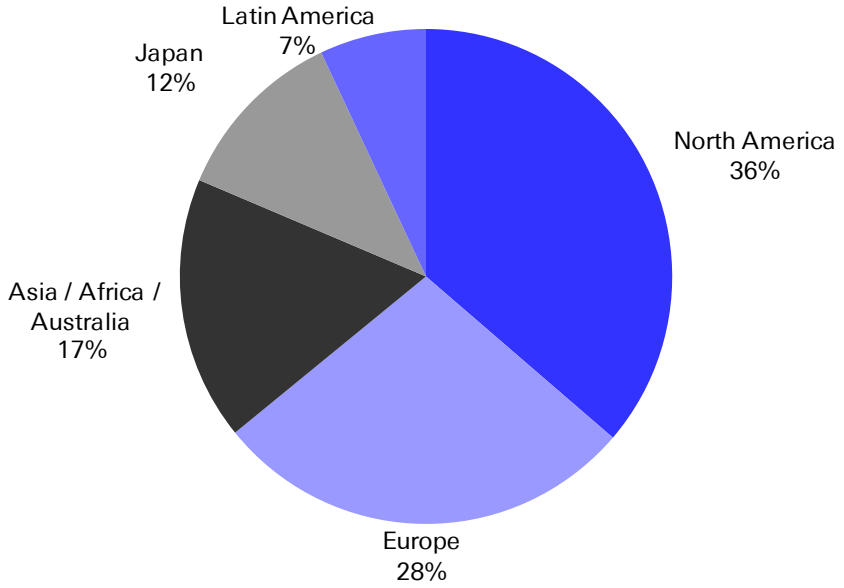
Source: IMS Health

On a regional basis, revenues from the US have grown in importance over these three decades and today account for around a third of total industry sales (Figure 2). US revenues gained not only from a more favourable pricing environment, but also strong patient demand supported by direct-to-consumer advertising. In contrast, government-influenced purchasing and formulary control have meant that the importance of European revenues as a percentage of the total industry has declined over the past 20 years. Today, Europe accounts for c.28% of global revenues. Similarly, the Japanese government's influence in domestic pharmaceutical markets has restricted the rate of absolute sales growth, with Japan today accounting for 12% of total sales.

Freedom of choice for patients (at least in relative terms), market-based pricing, and expanding insurance coverage in the US, compared with the tough pricing environment across Europe, suggest that the US will maintain its lead as the single most important market for pharmaceutical companies. However, US healthcare reform and the disproportionately greater impact of patent losses (generic erosion is significantly more rapid in the US than elsewhere) should constrain growth over time. Thus, much of global industry growth in the years ahead is likely to come from emerging markets, rather than these traditional developed markets. Currently emerging markets account for 20% of global industry sales. IMS Health estimates that around 70% of growth over 2011-2016 will come from the 'pharmerging' markets, including the so-called BRIC nations (Brazil, Russia, India, China) and other developing countries. China alone is expected to contribute 40% of the growth over this period, equivalent to c.$90 billion in

incremental revenues, so that by 2016, it will rank No. 2 by country sales, behind only the US.

Figure 2: Global pharmaceutical sales by region, 2011

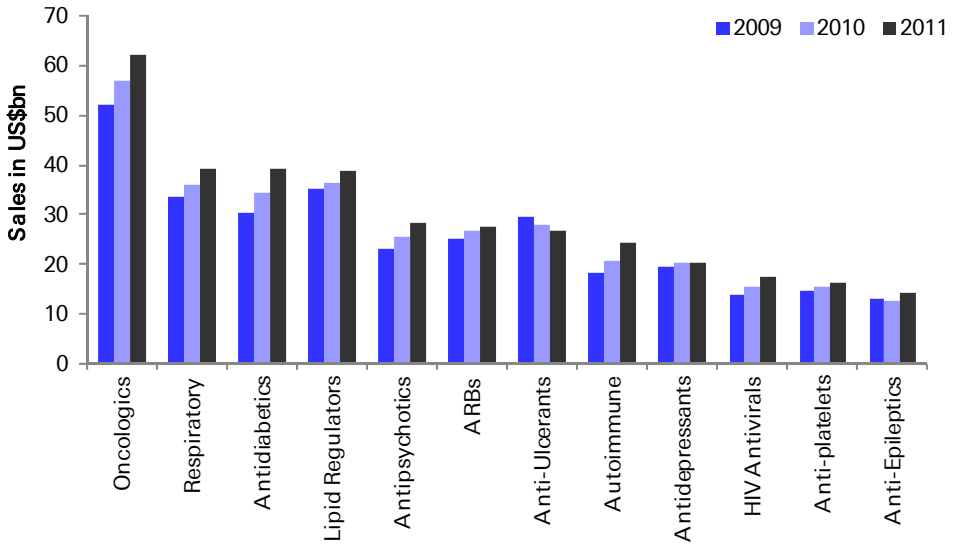


Source: IMS Health

Cardiovascular and oncology drugs lead sales

Looked at by therapy area, oncology drugs comprise the largest single category (Figure 3), driven by the emergence of important new treatments for various cancer types. When aggregated, the different sub-classes of cardiovascular drugs - notably the cholesterol-lowering agents, angiotensin-II receptor blockers (ARBs) for lowering blood pressure, and platelet aggregation inhibitors for preventing thrombosis - are more important still, accounting for close to 10% of industry sales. Respiratory drugs have also experienced strong growth in the past two decades, driven by increasing use of inhaled combination drugs for asthma and COPD, and rising disease awareness. The market for diabetes treatment is almost as large, having experienced double digit growth with the introduction of new classes of drugs in the past decade.

Figure 3: Pharmaceutical sales by category



Source: IMS Health

Consolidating, but still fragmented industry

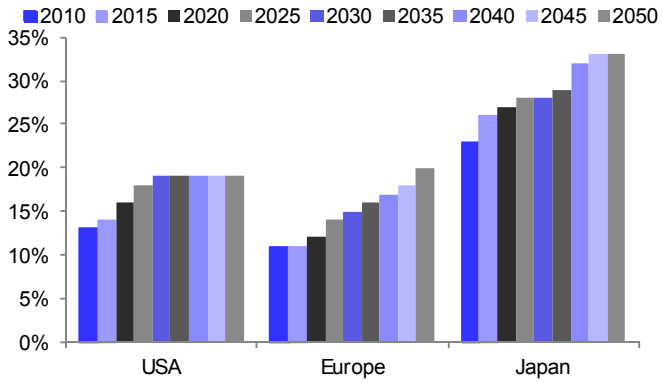
From a company perspective, the ability to fund innovation, together with industry consolidation, has meant that an increasing proportion of global sales are concentrated in the hands of the top ten players. This process accelerated with a wave of mega-mergers in the late 1990s creating the likes of Sanofi, AstraZeneca and GlaxoSmithKline, and again in the late 2000s, with the combinations of Merck and Schering-Plough, Roche and Genentech, and Pfizer and Wyeth. We estimate that the top ten pharmaceutical companies accounted for around 47% of industry revenues in 2011, compared with less than 25% three decades earlier. However, despite this consolidation, it is of note that the world's largest pharmaceutical company, Pfizer, still accounts for only 7.5% of industry revenues.

Growth drivers in a little more detail

Demographics (ageing population) to drive strong underlying demand

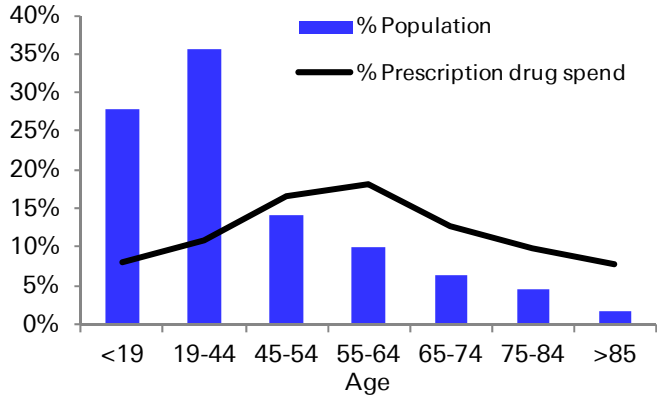
The world's developed economies are facing an ageing population: for every five years since 1965, approximately one additional year has been added to life expectancy at birth. In the US, for example, life expectancy at birth in 1920 was a modest 54 years. By 1965 it stood at 70 years, while today, the average life expectancy at birth stands at just over 78 years. Consequently, the number of elderly in the US and Europe is projected to increase by c.57% in the next 20 years (see Figure 4). Data from the National Centre for Health Statistics have shown that consumption of drugs and healthcare services increases proportionately with age (Figure 5 and Figure 6). Thus, with the proportion of elderly expected to rise in the coming years, the demand for drugs and healthcare services is also expected to increase. Furthermore, with the industrialization of emerging markets, and movement from fields to cities, not only should we see increased longetivity, but also fast changing demographics with an emergence of lifestyle related diseases.

Figure 4: Projected percentage of population >65 years



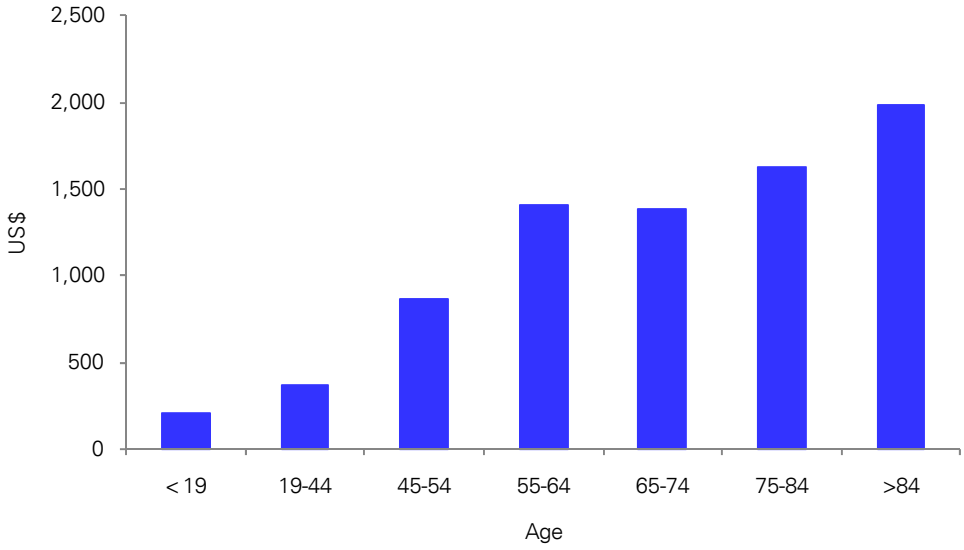
Source: World Bank

Figure 5: US prescription use and population by age



Source: Health, United States, 2010 (National Centre for Health Statistics)

Figure 6: US prescription drug expenditure per capita, by age



Source: Health, United States, 2010 (National Centre for Health Statistics)

Innovation to address unmet medical needs

As the pharmaceutical industry has grown, it has ploughed increasing amounts of money into R&D in search of new medicines to better treat disease. In the US alone, the industry trade body PhRMA (Pharmaceutical Research and Manufacturers of America) estimates that pharmaceutical R&D spending has increased more than twenty-fold over the past 30 years. As a consequence, more molecules than ever before are entering research pipelines (although failure rates have also risen substantially, as we discuss later). The number of compounds in clinical trials has increased from c.1,800 in 1999 to c.3,240 in 2011. We expect ongoing research to add to the body of knowledge surrounding the interaction of genes and proteins in different diseases, as well as our understanding of biological pathways. Such an increase in our knowledge of the body's chemistry, and with it the elucidation of potential new targets for therapeutic intervention, should drive a substantial increase in our ability to develop new medicines to treat and prevent disease.

Rising affluence of emerging markets

Emerging markets refers to a group of rapidly growing economies undergoing the transition from developing to developed nation status. This is typified by a group of

countries which IMS Health refers to as the "pharmerging countries". IMS divides these into tiers, with tier 1 solely represented by China (the world's number 3 market by sales), tier 2 being the other BRIC countries (Brazil, Russia, India) and tier 3 including a diverse range of smaller markets including Mexico, Turkey and Poland, among others. As the GDP per capita of these emerging economies increases, the ability of their governments and their population to afford new medicines also increases (note that out-of-pocket or private spending currently accounts for well over half of prescription sales in most of these markets). IMS Health projects that growth in pharmaceutical spend in Latin America, and in Asia, Africa and Australia will average 12-15% for 2012-16, compared with 1-4% in North America and a 1-2% decline in Europe (Figure 7).

Figure 7: Pharmaceutical market size and projected growth by region

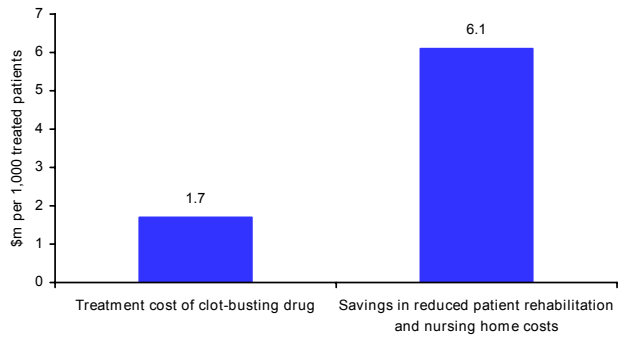
Region	2011 market size ($ bn)	2012-2016 CAGR
North America	344.4	1-4%
EU5	159.1	(-1)-2%
Japan	111.2	1-4%
Pharmerging	193.6	12-15%
RoW	147.1	2-5%
Global	**955.5**	**3-6%**

Source: IMS Health

Medicines are cost effective and help contain overall healthcare spend

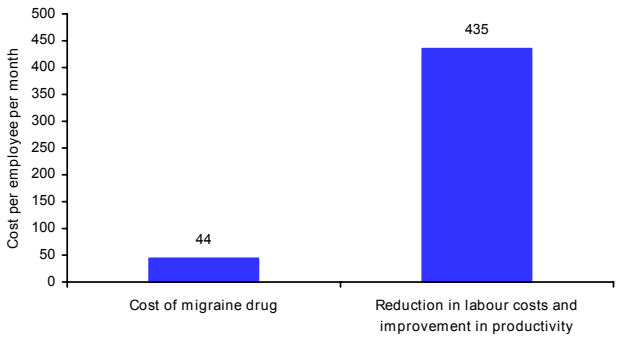
It is also worth noting that, relative to hospitalisation, surgery and lost productivity, pharmaceuticals represent a highly cost-effective means for governments and insurance companies to contain the healthcare costs of an ageing population (Figure 8 and Figure 9). Of course, the profitability of the industry makes it an easy target for governments as they seek to hold back the steadily rising costs of providing a healthcare system. However, the reality is that the use of pharmaceuticals saves society huge costs every year in the management of disease. Although this is more debatable (and emotive) in areas such as late-stage cancer, these benefits are clearly evident in areas such as cardiovascular disease and diabetes. As such, health economic arguments suggest that healthcare authorities around the world should increase rational use of pharmaceutical drugs if aggregate cost containment is to be achieved. In fact, organizations such as the UK's National Institute for Health and Clinical Excellence (NICE) have been formed with the explicit mandate of drafting guidelines and recommending therapies based on their aggregate economic benefit.

Figure 8: Cost vs. savings for anti-thrombotic ($m)



Source: Fagan FC et al (1998)

Figure 9: Cost vs. savings for migraine drugs ($)



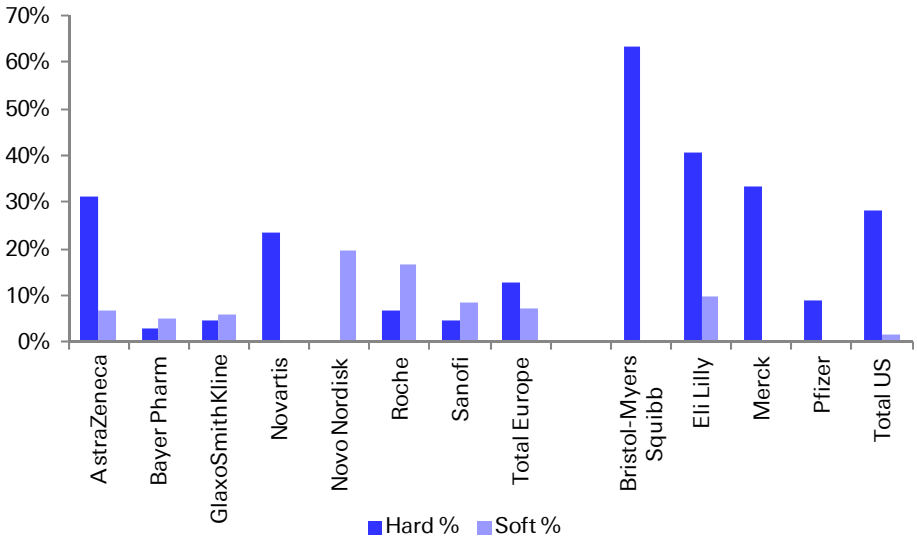
Source: Legg RF et al (1997)

Pressures also growing

Patent expiries the biggest near-term threat

Patent expiries and the subsequent loss of revenue due to generic competition are a fact of life for a research driven industry. However, the threat to revenues and profits has loomed large over the pharmaceutical industry in recent years. 2012 marks the toughest year of the so-called 'patent cliff' for both US and European large-cap pharma names, with the scale of fresh patent losses moderating over 2013-15. By 2016, c.$100 billion of 2011 pharmaceutical sales by large-cap pharmaceutical companies will be exposed to generic competition. Of this amount, about 21% may be deemed 'soft exposure', referring to the loss of patent protection of biologic products or complex delivery products (notably asthma inhalers and insulin delivery devices), which face slower generic erosion due to more stringent regulatory requirements for approval. This is in contrast to so-called 'hard exposure', which refers to the well-established process of approval of generic copies of chemical compounds, where erosion of sales is likely to occur very rapidly. With the FDA and EU regulators already positioned to approve biosimilars, much of the 'soft exposure' will also come under pressure in the coming years. Few pharmaceutical companies have a late-stage pipeline fully able to compensate for this expected drop in sales. Hence, we believe the revenues of several leading pharmaceutical companies will likely remain under pressure in the short term.

Figure 10: 2011-16 patent exposure as % of 2011 healthcare sales



Hard – chemical compound, likely fast generic erosion, Soft – biologic compound, unlikely to experience rapid generic erosion
Source: Company data, Deutsche Bank estimates

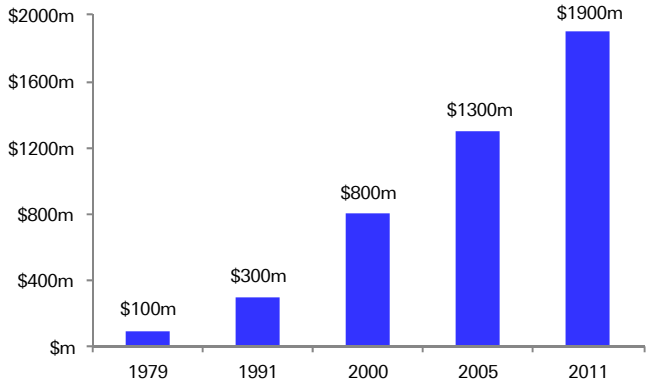
Rising R&D costs and falling productivity

R&D costs have continued to increase steadily, from 9% of industry sales in 1971 to nearly 17% of sales in 2011. Safety scares and high-profile drug withdrawals in the past decade, such as Merck's pain medication Vioxx and GlaxoSmithKline's Avandia, have resulted in heightened regulatory scrutiny of new drugs seeking marketing approval. As a result, clinical trials have required a greater number of patients and a longer observation period to assure regulators of the safety and efficacy of new drugs. The time and cost required for each study has increased proportionately with each stage of clinical trials.

Not surprisingly, this has led to a huge increase in the average costs incurred to develop a new drug. Industry consultants estimate that the average successful drug

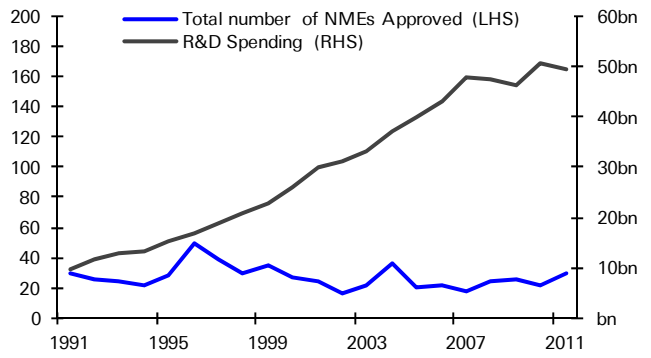
now costs $1.9 billion before tax to bring to market, allowing for the cost of drugs that fail along the development process (Figure 11). Unsurprisingly this has resulted in a burgeoning of R&D spend in the US over the past two decades (Figure 12), but not an accompanying rise in new drug approvals (although the average sales achieved by new drugs has increased through the period). According to an industry analysis by PhRMA, fewer than two in ten drugs eventually recoup the cost of development (Figure 13).

Figure 11: Costs of one approved new drug



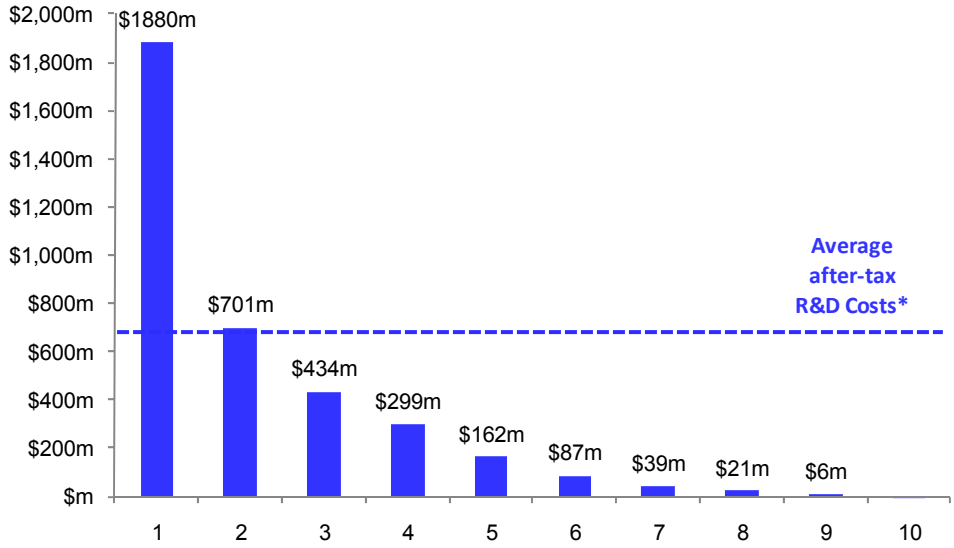
Source: J.A. DiMasi and H.G. Grbowski "The Cost of biopharmaceutical R&D: is Biotech Different?" Managerial and Decision Economics 2007, PhRMA, EvaluatePharma

Figure 12: R&D spend vs. drugs approved ($)



Source: PhRMA, FDA

Figure 13: Average after-tax PV of sales of approved FDA drugs in US (by deciles)

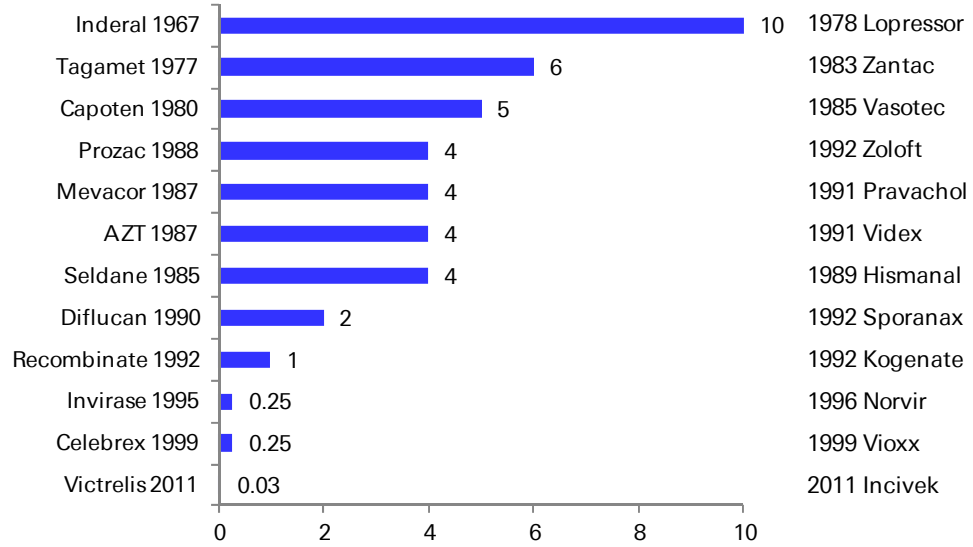


** Average R&D Costs include the cost of the approved medicines as well as those that fail to reach approval.*
Source: J. A. Vernon, J. H. Golec, and J. A. DiMasi, "Drug Development Costs When Financial Risk Is Measured Using the Fama-French Three-Factor Model," Health Economics Letters (2009); J. DiMasi and H. Grabowski, "The Cost of Biopharmaceutical R&D: Is Biotech Different?" Managerial and Decision Economics 28 (2007): 469–479, PhRMA

Market exclusivity in new classes shortening

Another feature of today's pharmaceutical market is that competition among drugs is increasing. Competitor drugs addressing the same medical condition via the same chemical pathway are entering the market at ever-faster rates. Where six years separated the launch of the ulcer drug Tagamet and its follower drug Zantac, only six months separated the launch of the first COX2 inhibitor, Celebrex, and the second to market, Vioxx. Today, innovator companies have much less time to maximise the potential of their innovation before same-class or 'me-too' drugs emerge.

Figure 14: Years separating first in class from first imitator



Source: PhRMA, The Wilkerson Group, Deutsche Bank

Government pricing intervention increasing

With the exception of the US, pharmaceutical prices in the developed world are predominantly determined by government-controlled authorities. As healthcare expenditures increase as a percentage of GDP and as governments of developed economies are faced with growing budget deficits, highly profitable pharmaceutical manufacturers are a convenient target upon which to impose cuts. Hence, drug prices are under regular review, with price or reimbursement cuts enforced in many countries, mostly prominently in Europe and Japan (Figure 15).

Figure 15: Revision rates on reimbursement prices in Japan

Year	1992	1994	1996	1997	1998	2000	2002	2004	2006	2008	2010	2012
Revision Rates	-8.1%	-6.6%	-6.8%	-3.0%	-9.7%	-7.0%	-6.3%	-4.2%	-6.7%	-5.2%	-5.8%	-6.3%

Source: Pharmaceutical Administration and Regulations in Japan by JPMA

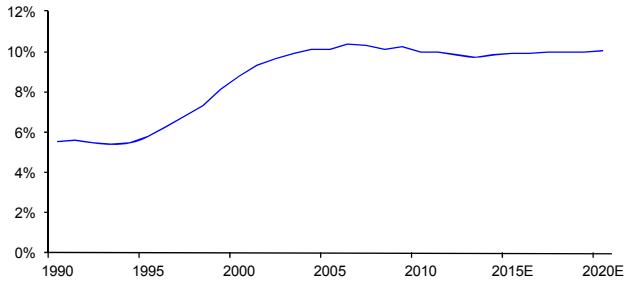
In addition, in several countries, a cost-benefit assessment is performed for high-priced pharmaceuticals before they may be considered for inclusion in the nation's formularies (which detail drugs that may be prescribed by doctors and health authorities), e.g. by NICE in the UK. Therefore, while an ageing society will result in growing demand for drugs, the cost pressures on society inevitably mean that governments will increase pressure on drug companies to reduce prices and encourage greater generic usage.

As in the aftermath of previous economic recessions, several European governments have responded to their fiscal deficits over the past two years by implementing price cuts on medicines, either directly or indirectly through a reduction in reimbursement. This has been given additional urgency by the austerity measures adopted in various Southern European countries as a result of the mounting debt crisis. Given that Europe accounts for 28% of global pharmaceutical spending, this has had a noticeable adverse impact on sales of pharma companies, further compounded by the reference pricing system (discussed under 'Funding and pricing of pharmaceuticals').

Even in the US, the high relative costs of drugs and rising medical insurance premiums are increasing pressure on the industry to contain price increases. Political pressure for containment of drug prices and industry profitability has also intensified in recent years, not least as the proportion of the health budget spent on drugs has risen at a faster rate

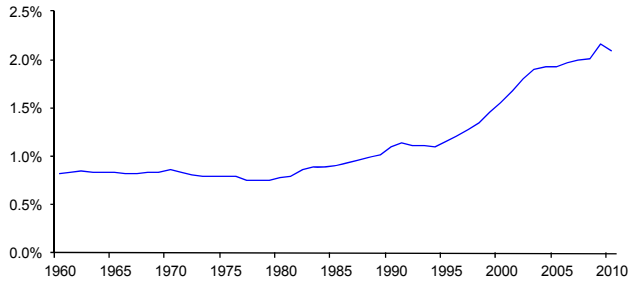
than healthcare expenditures overall and as drug price rises have exceeded CPI. Initiatives within the private sector to increase the percentage of overall drug cost borne by the consumer (co-pay) or to encourage therapeutic substitution (replacement of a branded drug by a similar but not identical drug that has lost patent protection) in certain therapy classes are having an effect on dampening market growth.

Figure 16: US pharma exp as % of national health exp



Source: Centers for Medicare & Medicaid Services

Figure 17: US pharma and non-durable exp as % of GDP



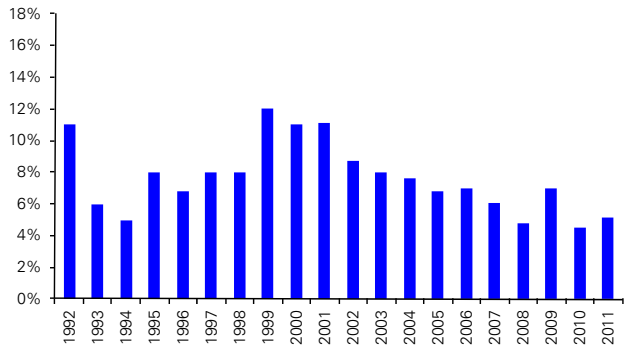
Source: OECD

Slowing global growth in drug sales

In conclusion, the long-term demand growth prospects for the pharmaceutical industry appear to be underscored by demographics and by the rapid ascent of emerging markets. However, near-term headwinds, notably patent losses and government (and payer) pricing pressures, will likely slow revenue growth over the next few years. In this respect, we note that IMS Health estimates that the pharmaceutical market will grow at an average rate of 3-6% pa over 2012-16, below the near 9% historic growth rate of the past three decades, while our own forecasts are near the mid-point of that range.

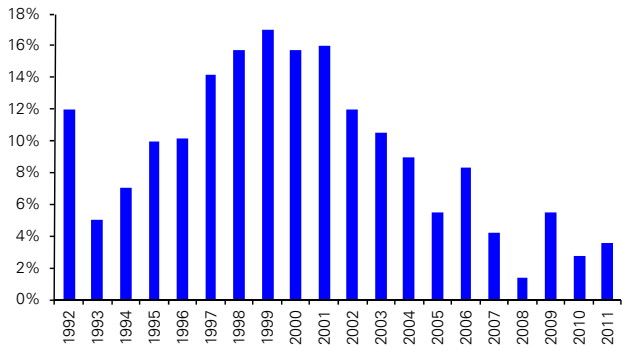
In the longer term, we remain optimistic that as the impact of blockbuster patent expiries lessens, the industry will once again maintain growth at rates exceeding global GDP growth based on innovation. With regard to the latter point, we are encouraged by evidence from a number of companies that ground-breaking science is alive and well, as seen by positive clinical and regulatory drug developments in the past few years from several leading companies (for example, in oncology and in diabetes).

Figure 18: Growth in global drug sales



Source: IMS Health

Figure 19: Growth in US drug sales



Source: IMS Health

The companies

US and European companies dominate

US and European pharmaceutical companies dominate today's pharmaceutical industry, as they have done through the last 30 years (Figure 20). The industry as a whole continues to be fragmented, however, with the top 10 companies accounting for c.47% of total sales and the top 20 companies accounting for c.66% of total sales.

A comparison of the league tables in 1981 and 2011 helps illustrate the extent to which mergers and acquisitions have shaped the industry. A number of well-known names have disappeared, to be replaced by their merged successors: Hoechst went on to be part of Sanofi, while Ciba-Geigy and Sandoz merged to form Novartis, and Wyeth is now part of Pfizer. All of today's top 10 companies have been involved in some form of major M&A activity in the past two decades. Despite this consolidation, over half of today's top 10 are in essence the same as those that led the tables in 1981, the newcomers being AstraZeneca, Johnson & Johnson and Abbott. It is also interesting to note that the world's leading generic pharmaceutical manufacturer, Teva, now lies just outside the top 10, and enjoys higher sales than traditional R&D-based powerhouses such as Bayer and Boehringer Ingelheim.

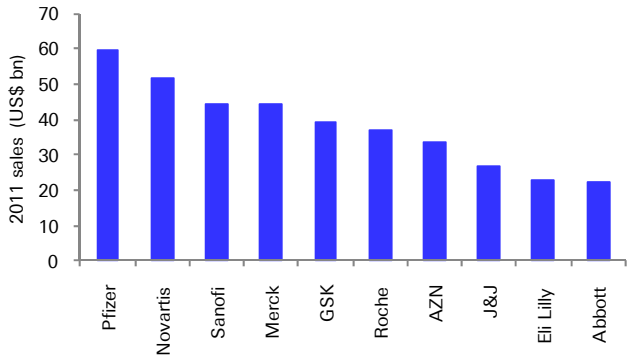
Figure 20: The 20 leading drug companies with pharmaceutical sales and market shares in 1981 and 2011

	----- 1981 -----			----- 2011 -----		
	Name	Sales ($ m)	Market share (%)	Name	Sales ($ m)	Market share (%)
1	Hoechst	2,559	3.7	Pfizer	59,353	7.4
2	Ciba-Geigy	2,103	3	Novartis	51,726	6.4
3	Merck & Co.	2,060	2.9	Sanofi	44,198	5.5
4	Roche	1,480	2.1	Merck & Co	44,052	5.5
5	Pfizer	1,454	2.1	GlaxoSmithKline	39,520	4.9
6	Wyeth	1,424	2.1	Roche	37,083	4.6
7	Sandoz	1,418	2.1	AstraZeneca	33,316	4.1
8	Eli Lilly	1,356	1.9	Johnson & Johnson	26,953	3.3
9	Bayer	1,225	1.8	Eli Lilly	22,608	2.8
10	SmithKline Beckman	1,220	1.7	Abbott Laboratories	22,435	2.8
11	Boehringer Ingelheim	1,100	1.6	Bristol-Myers Squibb	21,244	2.6
12	Takeda	1,082	1.6	Teva	18,233	2.3
13	Upjohn	1,042	1.5	Takeda	18,228	2.3
14	Johnson & Johnson	1,008	1.4	Bayer	17,537	2.2
15	Bristol-Myers	1,000	1.4	Boehringer Ingelheim	16,726	2.1
16	Schering-Plough	871	1.2	Amgen	15,582	1.9
17	Sankyo	868	1.2	Astellas Pharma	12,556	1.6
18	Rhone-Poulenc	825	1.2	Novo Nordisk	12,394	1.5
19	Shionogi	800	1.1	Daiichi Sankyo	11,543	1.4
20	Glaxo	784	1.1	Merck KGaA	8,931	1.1

Source: Company data, Deutsche Bank estimates

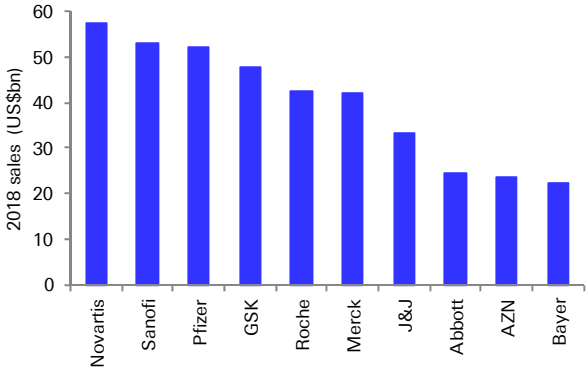
Figure 21 and Figure 22 show the top 10 companies by sales in 2011 and the projected top 10 in 2018, based on a compilation of analyst forecasts by the industry consultancy EvaluatePharma. This suggests that Novartis and Sanofi will displace the current industry leader Pfizer in the coming years.

Figure 21: 10 leading companies by pharma sales - 2011



Source: Evaluate Pharma

Figure 22: 10 leading companies by pharma sales - 2018



Source: Evaluate Pharma

Industry consolidation

M&A activity over the past two decades belies some strong underlying performances. For example, the combination of ICI's former pharmaceutical business, Zeneca, with the Swedish company, Astra, in 1999 created a business which in 1981 had little more than 1% of the global market, but by 2011 enjoyed over a 4% share. Less spectacularly, in 1981 the combined market share of Ciba-Geigy and Sandoz, which today comprise Novartis, was just over 5%, while the company's share in 2011 had risen to 6.4%.

In essence, the reasons for consolidation in the pharmaceutical industry are not dissimilar to those in other industries. We note the following reasons as being the main drivers of consolidation in recent years:

Patent expiry

Losing patent protection on a blockbuster drug that constitutes a significant proportion of sales can have a dramatic impact on profitability and growth. Mergers afford the opportunity to realise cost synergies, therefore compensating for income lost following patent expiry. In addition, they allow the opportunity to spread the revenue decline over a wider revenue base, thereby reducing the decline in earnings. Furthermore, mergers allow diversification of exposed business models into other, lower growth, but more sustainable areas of healthcare. Mergers that have been undertaken as a result of impending patent expiries include Glaxo's 1995 acquisition of Wellcome (Zantac patent expiry), Astra's 1999 merger with Zeneca (Losec and Zestril patent expiries), Pharmacia's 1995 merger with Upjohn (Halcion and Xanax patent expiries), Sanofi's merger with Aventis (Ambien and Eloxatin patent expiries, patent challenge to Plavix), and most recently, Pfizer's acquisition of Wyeth (impending expiry of Lipitor patent).

R&D costs

As the costs of discovering and bringing new drugs to market have increased, so too have the risks of failure and the need to have sufficient compounds in development to fund growth. In addition, the expanding breadth of developments in different therapeutic areas has led to growing research teams and burgeoning expenditure. Growing regulatory scrutiny of drugs now requires pharmaceutical companies to conduct longer clinical trials involving larger groups of patients. Mergers afford a sensible approach to consolidate research teams in the same therapeutic areas, and reduce costs while ensuring compounds continue to progress through the developmental pipeline. They can also help to address the problem of certain

companies having insufficient late-stage pipeline candidates or technology capabilities to address their impending patent losses.

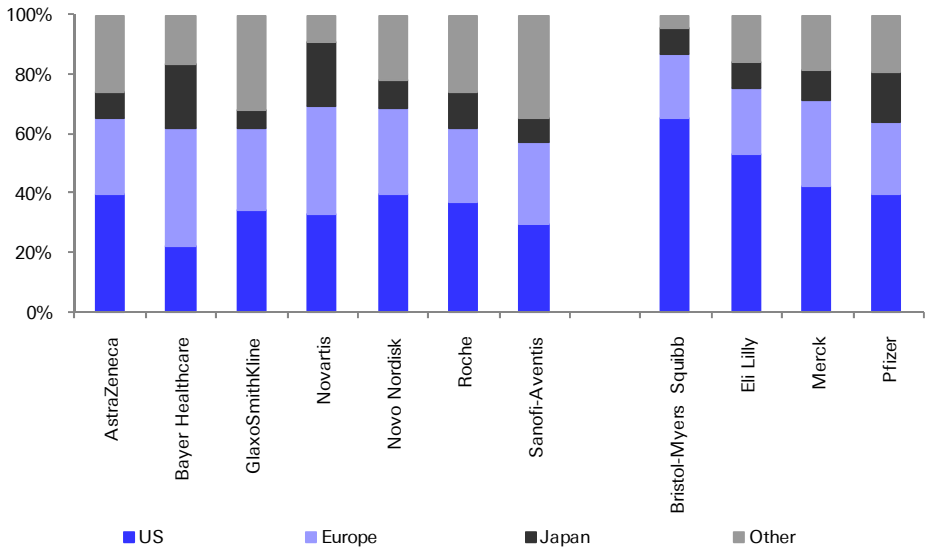
Marketing costs

The previous decade saw an 'arms race' among large pharmaceutical companies, which competed to have the largest sales force to ensure that drugs received intense marketing among physicians and consumers. This was notable in the US, in particular, although this is now happening in the emerging markets, most visibly in China. More recently, the loss of patent protection for key blockbuster drugs, either actual or impending, has forced companies to adopt a more rational approach to sales and marketing. Mergers allow companies to consolidate marketing and sales forces. For example, following the merger of Merck and Schering-Plough, the company announced a target to lay off 16,000 staff, mostly in duplication of sales force.

Geographic expansion

Rapid economic growth in emerging markets has presented pharmaceutical companies with attractive new opportunities in which to market their products. However, these companies require a local presence and infrastructure to distribute and market in each country. Acquisitions of local companies provide a means of quick access to the local market through an established sales force, distribution channels and local relationships.

Figure 23: Sales by geographic region, 2011



Source: Company data, Deutsche Bank estimates

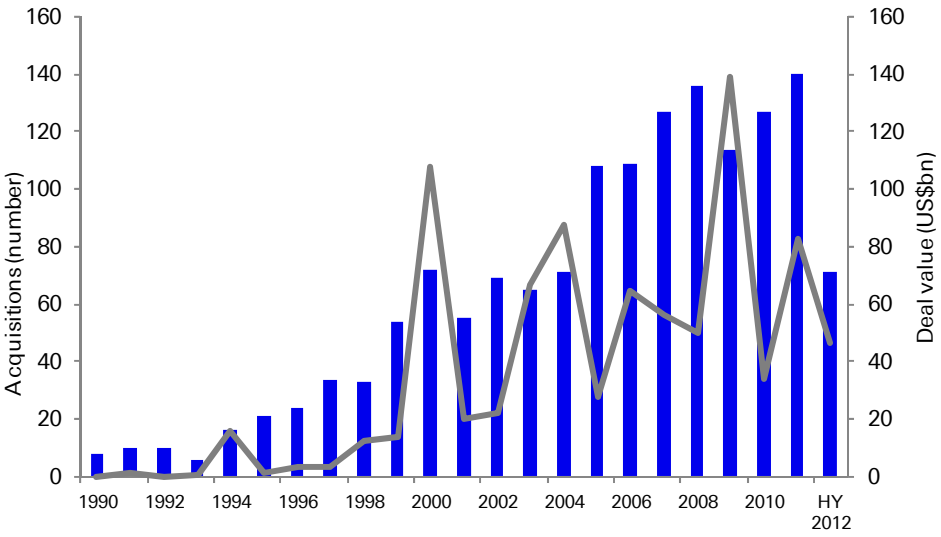
History of consolidation

Figure 25 lists some of the M&A transactions that have shaped the current landscape of the pharmaceutical industry. This indicates that, in addition to a steady background level of M&A, there were two periods of intense consolidation in the past decade or so, with a series of mega-mergers occurring between 1999 and 2000, and again in 2009-2011. Judging by the current run-rate, this trend is set to decline in 2012 as the industry focuses on getting past the worst of the patent cliff.

Following the recent wave of deals, the key question which remains is - What lies ahead? Will there be a pause as companies consolidate their acquisitions, integrate their operations and realise synergies? Or will there be more to come, as continued

revenue pressures from patent expiries and government price cuts drive further mergers? Or will we see demergers, with diversified business models becoming obsolete past the patent cliff?

Figure 24: Number of pharmaceutical industry acquisitions, 1985-2011



Source: EvaluatePharma

Figure 25: Summary of major industry transactions 1991-2012

Year	Purchaser	Target	Cost of target ($ bn)
2012	GlaxoSmithKline	Human Genome Sciences	3.0
2012	Bristol-Myers Squibb/ AstraZeneca	Amylin pharmaceuticals	7.0
2012	Gilead Sciences	Pharmasset	11.2
2011	Teva Pharmaceutical Industries	Cephalon	6.8
2011	Takeda	Nycomed	13.1
2011	Grifols	Talecris Biotherapeutics	3.4
2011	Sanofi	Genzyme	20.1
2010	Biovail	Valeant Pharmaceuticals Intl	4.5
2010	Teva Pharmaceutical Industries	ratiopharm	5.0
2010	Astellas	OSI	4.0
2010	Novartis	Alcon	49.7
2009	Roche	Genentech	46.8
2009	Merck	Schering-Plough	41.1
2009	Pfizer	Wyeth	68.0
2008	Eli Lilly	Imcline	6.5
2008	Takeda	Millennium	8.8
2007	AstraZeneca	MedImmune	15.0
2007	Schering-Plough	Organon	14.4
2006	Eli Lilly	Icos	2.1
2006	Merck KGaA	Serono S.A.	13.3
2006	UCB	Schwarz	5.6
2006	Bayer	Schering AG	20.5
2005	Sankyo	Daiichi	7.7
2005	Dainippon	Sumitomo	2.1
2005	Yamanouchi	Fujisawa	6.9
2004	Sanofi-Synthelabo	Aventis	72.7
2004	UCB	Celltech	2.4
2003	Pfizer	Pharmacia	64.3
2002	Amgen	Immunex	17.6
2001	Bristol-Myers	DuPont Pharma	7.8
2000	Johnson & Johnson	Alza	11.7
2000	Shire	Biochem Pharma	3.5
2000	Abbott	Knoll (BASF Pharma)	7.0
2000	Glaxo Wellcome	SmithKline Beecham	72.4
2000	Pfizer	Warner-Lambert	90.3
1999	Pharmacia Upjohn	Monsanto	26.9
1998	Rhone-Poulenc Rorer	Hoechst AG	21.2
1998	Sanofi	Synthelabo	9.2
1998	Zeneca	Astra	34.6
1997	Hoffmann-La Roche	Boehringer Mannheim	11.0
1996	Sandoz	Ciba-Geigy	60.0*
1995	Glaxo	Burroughs Wellcome	20.0
1995	Hoechst-Roussel	Marion Merrell Dow	7.1
1995	Pharmacia	Upjohn	13.0*
1995	Rhone-Polenc Rorer	Fisons	2.7
1995	American Home	American Cyanamid	9.2
1994	Hoffmann-La Roche	Syntex	5.3
1994	Sanofi	Sterling	1.9
1990	Beecham	SmithKline Beckman	6.5*

Source: Deutsche Bank estimates, Bloomberg Finance LP, *Value of merged entity

Therapeutic strengths indicate greater concentration

Despite substantial M&A activity, the industry in aggregate can still be described as fragmented. As discussed earlier, although market shares have concentrated, today's top ten companies still only account for c.47% of global market revenues (although this is substantially ahead of the comparable figure of 25% two decades earlier).

These simple statistics belie far greater market concentration if different therapeutic markets are considered. For example, the $17 billion insulin market is comprised almost entirely of three companies – Novo Nordisk, Sanofi and Eli Lilly. Similarly, in the $28 billion Asthma/COPD market, GlaxoSmithKline alone has a market share of nearly 40%. Consequently, while the industry may still be fragmented from a total market perspective, by therapeutic area, industry concentration is often much greater. Companies have most definitely established strong franchises in different therapeutic markets.

Importantly, these franchises have real value beyond economies of scale. Strong association with a particular disease inspires greater confidence in new drugs introduced by the franchise company. Equally, the franchise company will most likely be seen as an attractive candidate for in-licensing or co-marketing opportunities, providing it with the opportunity to further strengthen its position. However, if new products selling into the franchise market are not developed, franchises can also prove transient. As seen by GlaxoSmithKline's failure to build on its success with Zantac in the GI market, following the loss of patent protection, years of marketing investment in building a franchise can disappear rapidly. For reference, we summarise the current leaders in key therapeutic areas in Figure 38.

Pipelines and patent expiries

2011 was an important year for the industry with 30 NME approvals by the FDA. Though important newsflow/regulatory decisions are expected for all the pharma majors, many of the companies are also set to lose patent protection on large and important drugs over the 2012-2016 period. Looking through current company pipelines, it is evident that expected additional sales could be insufficient to replace the sales lost through patent expiries. Indeed, the pipelines of the major pharmaceutical companies have looked relatively thin for at least several years. This does not bode well for the growth prospects of many of today's industry leaders.

The following tables summarise the pipeline potential and expiry risks of the global majors. We note that US pharmaceutical companies have the largest exposure of sales to patent expiries, with c.30% of 2011 sales potentially vulnerable to generic competition by 2016. The risks of this patent cliff can be seen in the gap between sales of drugs expiring and those expected to launch from 2012 to 2016. However, we should note that this may overstate the true risk in some instances, as a small proportion of patent expiries (notably those on biologic drugs and those with complex delivery mechanisms, such as inhaled asthma drugs) are considered 'soft' expiries, where the impact is likely to be less severe.

Figure 26: Pipeline potential and patent exposure 2012-16

Company	2011 sales exposed patent expiry to 2016E ($ m)	Major expiry year	% 2011 sales lost to 2016E	2016 sales of launches ($ m)	Key launch year	2016E sales of launched drugs as % 2011 sales
European						
AstraZeneca	12,734	2012	37.9%	1,072	2012	3.2%
Bayer Pharm	1,889	2014	7.9%	2,223	2013	9.3%
GlaxoSmithKline	4,634	2013	10.4%	4,219	2013	12.8%
Novartis	13,741	2012	23.5%	1,748	2014	3.0%
Novo Nordisk	1,782	2014	14.4%	2,445	2012	19.7%
Roche	11,243	2015	35.0%	2,749	2012	7.4%
Sanofi	6,549	2015	14.1%	2,161	2012	4.6%
United States						
Bristol-Myers Squibb	13,478	2012	63.4%	3,675	2012	17.3%
Eli Lilly	12,219	2013	50.3%	760	2014	3.1%
Merck	15,950	2012	33.2%	4,065	2012	8.5%
Pfizer	5,920	2014	8.8%	NA*	NA*	NA*

Source: Company data, Deutsche Bank estimates,
**We are currently restricted on Pfizer*

European companies: Pipelines and expiries 2012-16E

Figure 27: AstraZeneca

Patent expiries	2011 Sales (US$ m)	% Sales	Expiry date
Seroquel (US, EU)	3,644	10.8%	Mar-12
Atacand (EU)	402	1.2%	2012
Symbicort (EU)	1,434	4.3%	2012
Zomig (US)	158	0.5%	May-13
Nexium (US)	2,397	7.1%	May-14
Symbicort (US)	846	2.5%	Oct-14
Crestor (US)	3,074	9.2%	Jul-16
Seroquel XR * (US)	779	2.3%	Nov-16

** Under patent settlement with Handa*

Pipeline	Indication	2016E Sales to company (Risk-adjusted, US$ m)	Expected WW Launch
Forxiga	Diabetes	238	2012, EU
Zinforo (ceftaroline)	Cephalosporin antibiotic	273	2012, EU
Fostamatinib (R788)	Rheumatoid arthiritis	338	2014
NKTR-118	Opioid-induced constipation	75	2014
Lesinurad	Hyperuricemia/gout	149	2015

Source: Company data, Deutsche Bank estimates

Figure 28: Bayer

Patent expiries	2011 Sales (Euro m)	% Sales	Expiry date
Avelox (US, EU)	486	2.8%	Mar-14
Kogenate (US)	290	1.7%	Dec-14
Mirena (US, EU)	581	3.4%	Dec-15

Pipeline	Indication	2016E Sales to company (Risk-adjusted, Euro m)	Expected WW Launch
Aletuzumab	Multiple sclerosis	48	2012
Alpharadin	Bone mets in cancer	967	2013
Regorafenib	CRC & GIST	307	2013
Riociguat	Pulmonary hypertension	275	2014
Long acting Factor VIII	Hemophilia A	NA	NA
Recombinant Factor VIIa	Hemophilia	NA	NA

Source: Company data, Deutsche Bank estimates

Figure 29: GlaxoSmithKline

Patent expiries	2011 Sales (£ m)	% Sales	Expiry date
Combivir (US)	127	0.5%	May-12
Agenerase (US)	74	0.3%	Dec-13
Advair/Servent (EU)	1,580	5.8%	Sep-13
Combivir (EU)	93	0.3%	2013
Lovaza (US)	567	2.1%	1Q-15
Avodart (US)	331	1.2%	4Q-15
Trizivir (US, EU)	117	0.4%	2016

Pipeline	Indication	2016E Sales to company (Risk-adjusted, £ m)	Expected WW Launch
Albiglutide	Type 2 diabetes	154	2013 US, 2014 EU
'436/'212 (Braf/Mek Inhibitors)	Cancer	413	2013
Dolutegravir	HIV	960	2013
Relvar/ Breo ('444/'698)	Asthma, COPD	480	2014
'444+'719	COPD	290	2014
MAGE-A3	Cancer	77	2014
Tyrisa	Atherosclerosis	256	2015
Otelixizumab	Rheumatoid arthiritis	NA	NA

Source: Company data, Deutsche Bank estimates

Figure 30: Novartis

Patent expiries	2011 Sales (US$ m)	% Sales	Expiry date
Diovan (US)	2,333	4.0%	Sep-12
Exforge (US)	325	0.6%	Sep-12
Femara (EU)	692	1.2%	Jan-12
Sandostatin LAR (EU)	869	1.5%	Nov-12
Exelon (US)	94	0.2%	Aug-12
Zometa (US, EU)	1,487	2.5%	2013
Aclasta (US, EU)	613	1.0%	2013
Stalevo (US, EU)	614	1.0%	2013
Sandostatin LAR (US)	574	1.0%	Jan-14
Afinitor (US)	199	0.3%	Sep-14
Glivec (US)	1,459	2.5%	Jul-15
Ritalin LA (US)	398	0.7%	Dec-15
Exforge (EU)	884	1.5%	2016
Glivec (EU)	3,200	5.5%	Jun-16

Pipeline	Indication	2016E Sales to company (Risk-adjusted, US$ m)	Expected WW Launch
Midostaurin (PKC412)	AML	48	2013
Serelaxin	Acute heart failure	170	2014, US
Seebri Breezehaler	COPD	425	2014, US
QVA149	COPD	1,080	2014
QMF149	COPD	25	2016
LBH589 (panobinostat)	Multiple myeloma	NA	NA
BAF312	Multiple sclerosis	NA	NA

Source: Company data, Deutsche Bank estimates

Figure 31: Roche

Patent expiries	2011 Sales (CHF m)	% Sales	Expiry date
Boniva (US, EU)	696	1.6%	2012
Xeloda (US, EU)	1,354	3.2%	2013
Rituxan (EU)	3,283	7.7%	Nov-13
Valcyte (US,EU)	569	1.3%	2015
Herceptin (EU)	3831	9.0%	2015
Tamiflu (EU)	199	0.5%	2016

Pipeline	Indication	2016E Sales to company (Risk-adjusted, CHF m)	Expected WW Launch
T-DM1	Breast cancer	1017	2013
Lebrikizumab	Asthma	294	2014
MetMAb	Lung cancer	668	2015
RG1678	Schizophrenia	253	2015
GA101	Lymphoma	49	2016
Ocrelizumab	Multiple sclerosis	147	2016
Aleglitezar	Type 2 diabetes	NA	NA

Source: Company data, Deutsche Bank estimates

Figure 32: Sanofi

Patent expiries	2011 Sales (Euro m)	% Sales	Expiry date
Plavix (US)	196	0.6%	May-12
Aprovel (EU)	753	2.3%	Aug-12
Hectorol (US)	148*	0.4%	Feb-14
Renagel/ Renvela (US, EU)	480	1.4%	2014
Lantus (EU)	730	2.2%	Nov-14
Lantus (US)	2336	7.0%	Feb-15
Fabrazyme (US)	61	0.2%	Sep-15

**Estimate*

Pipeline	Indication	2016E Sales to company (Risk-adjusted, Euro m)	Expected WW Launch
Kynamro	Hypercholesterolemia	267	2013
Lemtrada	Multiple sclerosis	336	2012
Omrabulin	Sarcoma	50	2013
Lyxumia	Type 2 Diabetes	301	2013
otamixaban	ACS	100	2013
Aubagio	Multiple sclerosis	210	2013
Eliglustat	Gaucher disease	139	2014
Anti-PCSK9	Hypercholesterolemia	150	2016

Source: Company data, Deutsche Bank estimates

Figure 33: Novo Nordisk

Patent expiries	2011 Sales (DKK m)	% Sales	Expiry date
NovoLog	6735*	10.2%	Dec-14
NovoLog Mix	2801*	4.2%	Dec-14

**Estimates*

Pipeline	Indication	2016E Sales to company (Risk-adjusted, DKK m)	Expected WW Launch
Degludec (Tresiba)	Diabetes	10039	2013
Degludec Plus (Ryzodec)	Diabetes	2008	2013
Factor VIII	Haemophilia A	1040	2014

Source: Company data, Deutsche Bank estimates

US companies: Pipelines and expiries 2012-16E

Figure 34: Bristol-Myers Squibb

Patent expiries	2011 Sales (US$ m)	% Sales	Expiry date
Plavix	7,087	33.4%	May-12
Avapro/ Avalide	952	4.5%	Mar-12
Baraclude	1,196	5.6%	Feb-15
Sustiva/ Atripla	1,485	7.0%	Mar-15
Abilify	2,758	13.0%	Apr-15

Pipeline	Indication	2016E Sales to company (Risk-adjusted, US$ m)	Expected WW Launch
Eliquis	Anti-platelet	2350	2013
Dapagliflozin	Type 2 diabetes	200	2013
BMS 700052	HCV	500	2015
BMS 708163	Alzheimer's disease	325	2015
PEG-rIL29	HCV	150	2016

Source: Company data, Deutsche Bank estimates

Figure 35: Eli Lilly

Patent expiries	2011 Sales (US$ m)	% Sales	Expiry date
Humalog	2,368	9.8%	May-13
Cymbalta	4,161	17.1%	Dec-13
Evista	1,068	4.4%	Mar-14

**Cymbalta patent expiration assumes 6-month pediatric extension*

Pipeline	Indication	2016E Sales to company (Risk-adjusted, US$ m)	Expected WW Launch
Ramucirumab	Cancer	100	2014
LY2189265 (dulaglutide)	Type 2 diabetes	315	2014
LY2127399 (Tabalumab)	Lupus, RA, multiple myelom	160	2014
LY2439821 (Ixekizumab)	Psoriasis, RA, ank. spondyliti	140	2015
Enzastaurin	Lymphoma	45	2015

Source: Company data, Deutsche Bank estimates

Figure 36: Merck

Patent expiries	2011 Sales (US$ m)	% Sales	Expiry date
Singulair	5,478	11.4%	Aug-12
Clarinex	621	1.3%	Jan-12
Maxalt	638	1.3%	Dec-12
Crixivan/Stocrin	192	0.4%	May-12
Temodar	934	1.9%	Aug-13
Propecia	447	0.9%	Jun-13
Avelox	322	0.7%	Mar-14
Integrilin	230	0.5%	Jun-15
Puregon	530	1.1%	Jun-15
Emend	419	0.9%	Apr-15
Remicade	2,667	5.6%	Jul-05
Cancidas	639	1.3%	Jul-15
Invanz	405	0.8%	May-16
Zetia	2,428	5.1%	Dec-16

Pipeline	Indication	2016E Sales to company (Risk-adjusted, US$ m)	Expected WW Launch
Bridion	Muscle relaxant reversal	1125	2012 EU, 2013 US
Tredaptive	Atherosclerosis	550	2012
Brinavess	Atrial fibrillation	190	2013, ex-US/EU
Suvorexant	Insomnia	675	2013
Elonva	Ovarian stimulation	400	2013
Odanacatib	Osteoporosis, bone mets	800	2014
Preladenant	Parkinson's disease	125	2015
MK 5172	HCV	200	2016

Source: Company data, Deutsche Bank estimates

Figure 37: Pfizer

Patent expiries	2011 Sales (US$ m)	% Sales	Expiry date
Geodon	1,022	1.5%	Mar-12
Revatio	535	0.8%	May-12
Detrol	557	0.8%	Sep-12
Celebrex	2523	3.7%	May-14
Zyvox	1283	1.9%	May-15

Pipeline	Indication	2016E Sales to company (Risk-adjusted, US$ m)*	Expected WW Launch
Tofacitinib	Rheumatoid arthiritis, psoriasis	NA	2012
Bosutinib	Chronic myelogenous leukemia	NA	2012
Dacomitinib	Lung cancer	NA	2014
Bazedoxifene	Osteoporosis	NA	NA

*Source: Company data, Deutsche Bank estimates, *We are currently restricted on Pfizer*

Figure 38: Therapeutic strengths and key products of the leading global pharmaceutical companies, 2011

	Anti-infective	Blood	Cardiovascular	CNS	Endocrine	Genito-Urinary	Musculoskeletal	Oncology	Respiratory	Other
Amgen		Aranesp, Epogen XX					Enbrel XX			Neulasta, Neupogen XXX
Astellas Pharma			Lipitor, Micardis XXX			Vesicare X				Prograf X
AstraZeneca			Crestor, Atacand XXX	Seroquel XXX				Zoladex X	Symbicort Turbuhaler XX	Nexium XX
Bayer		Kogenate X		Betaseron X		Yasmin/YAZ X		Nexavar X		
Eli Lilly				Zyprexa, Cymbalta XXX	Humalog X	Cialis X	Evista X	Alimta X		
GlaxoSmithKline	Augmentin,Pediarix,Hep.Vaccines XX					Avodart X			Seretide, Flixotide XXX	Consumer Health XXX
Johnson & Johnson	Prezista X	Procrit/Eprex X		Risperdal, Tylenol, Concerta XX			Remicade XX	Velcade X		
Merck & Co	Isentress, Gardasil X		Zetia, Vytorin, Cozaar XXX		Januvia, Janumet XX		Remicade XX		Singulair, Nasonex XXX	
Novartis		Enoxaparin X	Diovan, Exforge XXX	Exelon X	Sandostatin LAR X		Zometa X	Gleevec XX		Lucentis, Generics, Consumer Health XXX
Novo Nordisk		NovoSeven X			Insulins, Victoza XXX					
Pfizer	Prevnar 13, Zyvox XX		Lipitor, Norvasc XXX	Lyrica, Geodon XX		Viagra, Premarin X	Enbrel, Celebrex XX	Sutent X		Xalatan X
Roche	Pegasys X						Rituxan, Avastin, Herceptin, Xeloda, Tarceva XXX			Lucentis, CellCept, Diagnostics XXX
Sanofi	PENTAct-HIB, Fluzone X	Lovenox X	Plavix, Avapro XXX		Lantus XXX			Eloxatin, Taxotere X		Animal Health, Generics, Rare disease XX

Source: Company data, Deutsche Bank estimates

Leading drugs

Top 10 drugs account for c.10% of industry revenues

The past decade has seen a dramatic increase in the number of blockbuster drugs - those achieving sales over $1 billion. In addition, the proportion of global industry revenues represented by the top ten drugs has increased from around 5% in 1985 to around 10% today. The world's largest drug in 2011, Pfizer's Lipitor, alone accounted for c.1% of industry revenues, although it lost patent protection in the US in November.

Figure 39 shows the world's best-selling drugs by global sales. Given the economies of scale and operational leverage associated with a product achieving blockbuster sales, the increase in number of such products has bolstered industry profitability over the last decade. Despite consolidation, the absolute size of key drugs suggests that pharmaceutical portfolios remain as exposed to patent expirations on large products today as was the case a decade ago.

Figure 39: World's leading drugs by revenues

Rank	Product	Indication	Company	2011 sales ($ bn)
1	Lipitor	Hyperlipidaemia	Pfizer	9.6
2	Seretide	Asthma	GlaxoSmithKline	8.1
3	Humira	Rheumatoid arthiritis	Abbott Laboratories	7.9
4	Plavix	Anti-thrombotic	Bristol-Myers Squibb	7.1
5	Rituxan	Oncology	Roche	6.8
6	Crestor	Hyperlipidaemia	AstraZeneca	6.6
7	Avastin	Oncology	Roche	6.0
8	Herceptin	Oncology	Roche	5.9
9	Seroquel	Schizophrenia	AstraZeneca	5.8
10	Diovan	Hypertension	Novartis	5.7
11	Singulair	Asthma	Merck & Co	5.5
12	Lantus	Diabetes	Sanofi	5.5
13	Abilify	Schizophrenia	Otsuka Holdings	5.3
14	Zyprexa	Schizophrenia	Eli Lilly	4.6
15	Nexium	Proton Pump Inhibitor	AstraZeneca	4.4
16	Spiriva	COPD	Boehringer Ingelheim	4.4
17	Cymbalta	Depression	Eli Lilly	4.2
18	Neulasta	Immunostimulant	Amgen	4.0
19	Enbrel	Rheumatoid arthiritis	Amgen	3.7
20	Lyrica	Neuropathic pain	Pfizer	3.7

Source: EvaluatePharma, Deutsche Bank estimates

Statins to lose their crown; biologics in ascendance

The first product to achieve annual sales of over $1 billion was SmithKline's anti-ulcer drug, Tagamet, in 1986. By 1990, seven drugs had attained blockbuster status. In 2011, over 100 drugs achieved sales of over $1 billion, with the top 13 drugs each achieving sales of over $5 billion.

Until 2001, a drug for gastric ulcers/acid reflux had for 15 years consistently topped the list of industry best sellers (Tagamet, followed by GSK's Zantac, then AstraZeneca's Prilosec). However, the rapid growth of the cholesterol-lowering drugs, such as Pfizer's

Lipitor and Merck's Zocor, combined with Prilosec's patent expiry, saw statins emerge as the industry leader. With patent expiries in the class dampening growth (Zocor's US patent expired in 2006, Lipitor's in 2011), biologic compounds such as monoclonal antibodies (oncology) and TNF inhibitors (used in rheumatoid arthritis and Crohn's disease) are in ascendance (Figure 40). According to projections by analysts compiled by Thomson Reuters, 7 of the top 10 best-selling drugs in 2012 will be biologics, the exceptions being AstraZeneca's statin Crestor, GlaxoSmithKline's respiratory drug Advair and Bristol-Myers Squibb's schizophrenia drug Abilify (Figure 41).

Figure 40: Consensus estimates of analysts' sales forecasts

	Top drugs in 2011	Company	Sales ($ bn)		Top drugs in 2018	Company	Sales ($ bn)
1	Lipitor	Pfizer	9.6	1	Avastin	Roche	7.6
2	Seretide	GlaxoSmithKline	8.1	2	Humira	Abbott Laboratories	7.2
3	Humira	Abbott Laboratories	7.9	3	Revlimid	Celgene	6.8
4	Plavix	Bristol-Myers Squibb	7.1	4	Prevnar 13	Pfizer	6.7
5	Rituxan	Roche	6.8	5	Rituxan	Roche	6.3
6	Crestor	AstraZeneca	6.6	6	PSI-7977	Gilead Sciences	6.1
7	Avastin	Roche	6.0	7	Seretide/Advair	GlaxoSmithKline	6.0
8	Herceptin	Roche	5.9	8	Lantus	Sanofi	5.9
9	Seroquel	AstraZeneca	5.8	9	Januvia	Merck & Co	5.8
10	Diovan	Novartis	5.7	10	Herceptin	Roche	5.4

Source: EvaluatePharma

Figure 41: Consensus estimates of analysts' sales forecasts

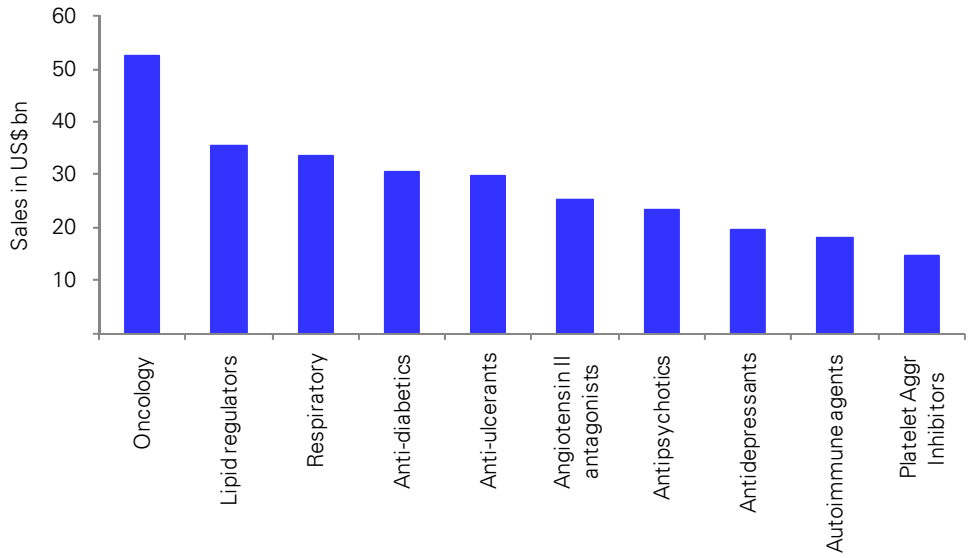
Drug	Projected 2012 sales ($ bn)	Company	Primary indications	Drug type
Humira	$9.3	Abbott Laboratories	Rheumatoid arthritis, Crohn's disease, psoriasis, ankylosing spondylitis	Antibody
Remicade	$9.1	Johnson & Johnson	Rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, ankylosing spondylitis	Antibody
Enbrel	$8.1	Amgen	Rheumatoid arthritis, psoriasis, juvenile idiopathic arthritis, ankylosing spondylitis	Antibody
Advair	$8.0	GlaxoSmithKline	Asthma, chronic obstructive pulmonary disease	Small molecule
Rituxan	$7.1	Genentech/Roche	Blood cancers, rheumatoid arthritis	Antibody
Crestor	$7.0	AstraZeneca	Cardiovascular disease	Small molecule
Avastin	$6.1	Genentech/Roche	Various cancers	Antibody
Herceptin	$6.1	Genentech/Roche	Breast cancer	Antibody
Lantus	$5.9	Sanofi	Diabetes	Protein
Abilify	$5.9	Bristol-Myers Squibb	Schizophrenia, bipolar disorder and depression	Small molecule

Source: Thomson Reuters Pharma, Nature Medicine

Dominant therapeutic categories

Examining industry revenues by therapeutic class, it is evident that the most significant categories are those for oncology (cancer) products, respiratory drugs (primarily asthma and COPD inhalers), anti-diabetics and cholesterol regulators (primarily statins). Each of these categories includes drugs which target a large and growing patient population. In particular, oncology drugs stand out as the major class. Of the world's 20 best-selling drugs, four are oncology drugs; sales of oncology drugs exceeded $60 billion in 2011, with a CAGR of c.15% over the last five years. Note that patent expiry of a best-selling drug can have a significant effect on sales of other drugs in that class (via 'therapeutic substitution'), as evidenced by the slowdown in growth of Lipitor and the statin class following the arrival of cheap generic copies of Zocor.

Figure 42: Leading therapeutic categories by sales, 2011



Source: IMS Health

Blockbusters of tomorrow

What will the new blockbusters of tomorrow be? Looking at current pipelines, the list of candidates appears rather limited. Aside from the multitude of second-generation and me-too products in development, some of the more interesting and innovative products include the following.

Cancer drugs

Looking ahead, an ageing population will most likely lead to higher incidence of cancer, which means that the growth in demand in the oncology class should continue in the coming years. However, a one-size-fits-all approach does not necessarily work in treating cancer. Hence, there is potential for many different drug therapies, depending on genetic make-up. Novartis' leukaemia drug Glivec was the first targeted cancer agent (in 2001), and the search for further, more rationally designed drugs continues. Roche has three Phase III targeted oncology drugs in the pipeline: T-DM1 and Pertuzumab for breast cancer and Onartuzumab for lung cancer. Bayer's alpharadin for bone metastases in prostate cancer is also a form of targeted therapy that permits high efficacy with minimal side effects.

Diabetic therapies

Diabetes is a major risk factor for cardiovascular disease, and by itself is a major metabolic disease. There is at present no cure for diabetes, and current therapies have helped in controlling the symptoms but not the progression of the disease. New therapies in the pipeline attempt to address the disease using novel pathways. Sodium-dependent glucose co-transporter (SGLT) inhibitors target a new pathway, reducing blood glucose levels by blocking the re-absorption of glucose from the renal filtrate. Candidates include Bristol-Myers Squibb/AstraZeneca's dapagliflozin and Johnson & Johnson's canagliflozin, which have shown promising efficacy in late-stage clinical trials, although questions exist about infection risk in the urinary tract (and the FDA has thus far resisted approving dapagliflozin). GlaxoSmithKline's albiglutide and Eli Lilly's dulaglutide join the ranks of GLP-1 agonists that have lower hypoglycemia risk vis-à-vis other diabetes therapies, in addition to weight loss benefits and weekly dosage

schedules. Focus is also now on improving convenience of therapy; Tresiba, Novo Nordisk's daily basal insulin, is expected to be launched in 2013, with benefit of flexible dosing schedules. Dual PPAR agonists, such as Roche's aleglitazar, stimulate PPAR receptors which increase insulin sensitivity and HDL cholesterol, while reducing triglycerides and LDL cholesterol. This therapy is risky, given the failure of an earlier candidate, muraglitazar by Bristol-Myers Squibb, and the controversy surrounding PPAR agonist, Avandia.

COPD drugs

Chronic obstructive pulmonary disorder (COPD) is primarily caused by smoking, and is a leading cause of death globally. Though there is no cure for COPD, existing therapies help relieve symptoms and improve quality of life. The emergence of new LABA/LAMA (long acting beta agonist + muscarinic antagonist) combination drugs could result in a improvement in standards of COPD therapy. GSK's '719+'444, Novartis' QVA149 (NVA237+QAB149) and Boehringer Ingelheim's tiotropium/olodaterol combination are all in phase III studies. However, in the absence of conclusive studies that support the efficacy of once-daily dosing for these combinations, their fate is yet uncertain. GlaxoSmithKline's Relvar is a LABA/ICS combination, a follow-on to its multi-$bn selling respiratory drug (and category leader), Advair.

Drugs for Alzheimer's disease

Alzheimer's disease is a debilitating disease that usually occurs in the elderly, for which there is no effective treatment. Given the projected global increase in the elderly population, there is a large and growing unmet need, presenting a potentially lucrative opportunity for pharmaceutical companies that are able to produce a successful therapy. Thus far, the disease has seen a series of only modestly effective drugs launched (namely the cholinesterase inhibitors, including Pfizer/Eisai's Aricept and Novartis' Exelon). Novel late-stage drugs have seen a high rate of failures, most recently with J&J/Elan's bapineuzumab failing to demonstrate an improvement on its primary endpoints in Phase III trials. The future of Lilly's solanezumab is also in doubt after it failed to meet primary endpoints in two Phase III studies. However, analyses of pooled data across both studies showed a statistical significant slowing of cognitive decline overall and in the subgroup of patients with mild Alzheimer's disease. Other high-profile setbacks include Dimebon (Pfizer/Medivation), which failed to differentiate from placebo in Phase III trials, and semagacestat (Eli Lilly), where results from Phase III studies showed a failure to slow disease progression and an increased risk of skin cancer. Current pipeline therapies include BMS-708163, a Phase II gamma secretase inhibitor from Bristol-Myers Squibb that prevents synthesis of amyloid protein. Intravenous immunoglobulins are also found to have high concentration of anti-amyloid antibodies and are being investigated for use in Alzheimer's. Separately, symptomatic drug treatments are still being developed, with Lundbeck and GlaxoSmithKline developing 5-HT6 receptor antagonists.

Cardiovascular drugs

Cardiovascular disease continues to be a leading cause of mortality in developed countries. With ageing demographics in developed economies, and changes in diet and lifestyle associated with increasing affluence in emerging markets, the problem looks likely to increase in coming years. Needless to say, novel effective therapies for cardiovascular disease could become blockbusters. In this area, there are several promising but relatively high-risk therapies in late-stage clinical studies. Merck's anacetrapib and Lilly's evacetrapib are cholesteryl-ester transfer protein (CETP) inhibitors, which aim to raise the levels of 'good' (HDL) cholesterol, and potentially reverse the narrowing of arteries. However, there is a lack of studies to definitively link higher HDL cholesterol to improved cardiovascular outcomes. Earlier CETP drug

candidates – torcetrapib, and most recently Roche's dalcetrapib, were unable to demonstrate efficacy. GlaxoSmithKline's darapladib, a lipoprotein-associated phospholipase A2 (lp-PLA2) inhibitor, targets a different pathway (lp-PLA2 is thought to be an independent risk factor for atherosclerosis) and aims, in conjunction with statins, to stabilize plaques in arteries, reducing plaque ruptures which lead to strokes and heart attacks. Sanofi also has two new compounds for familial hypercholesterolemia in its pipeline: mipomersen is a Phase III apolipoprotein B synthesis inhibitor, while anti-PCSK9 is a Phase III drug that targets cholesterol homeostasis.

Figure 43: Medicines in development in 2012

Therapeutic Category	Number
Cancer	948
-Lung Cancer	*141*
-Breast Cancer	*132*
-Colorectal Cancer	*85*
-Skin Cancer	*85*
Rare Diseases*	460
Respiratory Disorders	398
Mental Disorders	255
Cardiovascular Disorders	252
Diabetes Mellitus	212
Leukemia	139
HIV/AIDS	88
Arthritis	76
Alzheimer's Disease	72
Parkinson's Disease	24

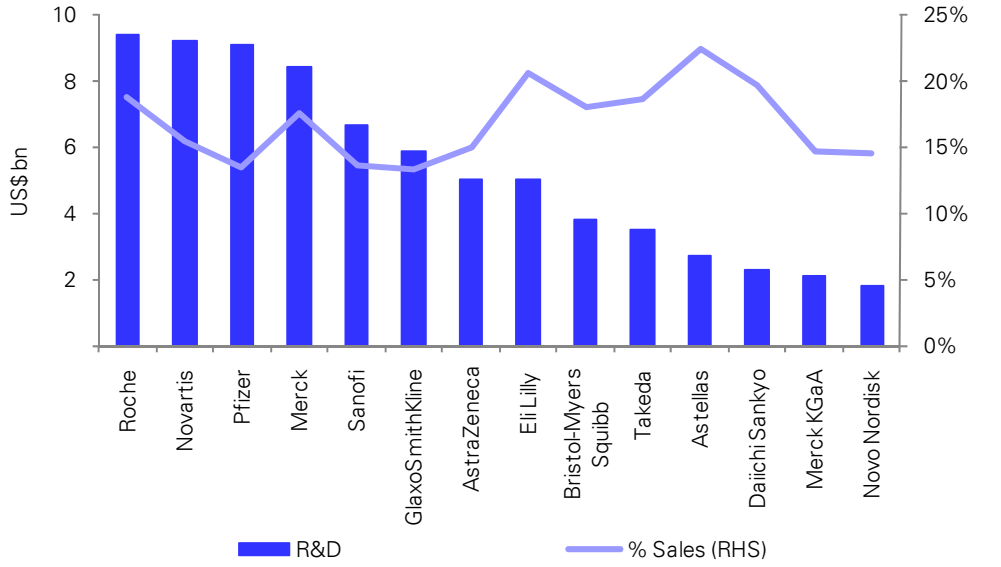
Source: PhRMA

Research

The R&D process

Research and development (R&D) is the lifeblood of the industry. It is only through innovation and the launch of new and effective forms of medicine that the pharmaceutical industry can continue to grow over the long term. Consequently, the major pharmaceutical companies have continued to devote a substantial proportion of their revenue to research and development over the past decade (Figure 44). EvaluatePharma estimates that the pharmaceutical industry spent c.$134.4 billion on research in 2011 (equivalent to c.18% of global pharmaceutical sales).

Figure 44: 2011 R&D expenditure by company



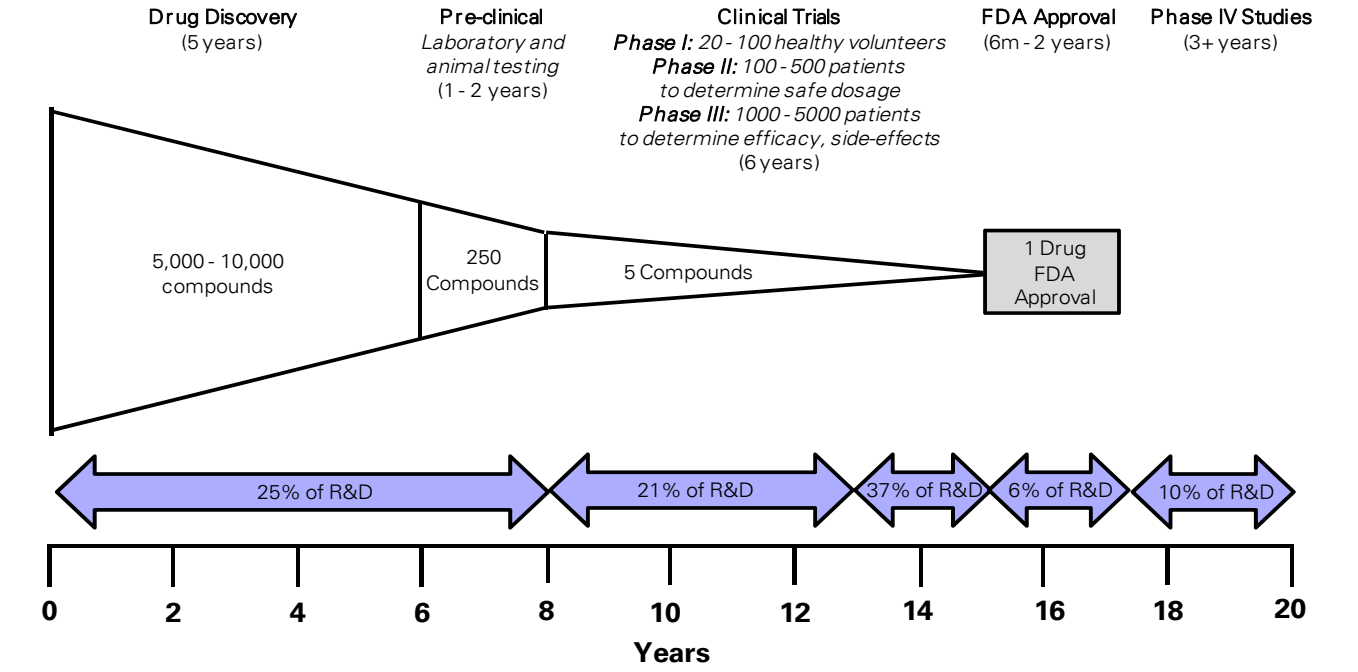
Source: Company data, Deutsche Bank estimates

The drug discovery process is clearly time consuming, complex and highly risky. From start to finish, PhRMA estimates suggest that of the 5,000-10,000 molecules screened in the discovery process, only one will make it to market as an approved drug. As molecules become more complex and safety regulations more stringent, the costs associated with developing a pharmaceutical have increased dramatically. A recent analysis from EvaluatePharma suggests that average cost of developing a successful new drug (NME or biologic) has risen to $1.9 billion in 2011, compared with a 2005 PhRMA estimate of $1.3 billion. This compares with an average $140 million in 1970s ($560 million in 2011 terms, inflation-adjusted). Similarly, the time taken from discovery to market has increased dramatically over the past 20 years, rising from around 11 years in 1980 to nearer 15 years today.

As illustrated in Figure 45, the R&D program for drug development comprises several distinct phases that can be broadly divided into discovery, pre-clinical, clinical and post-marketing. On average, we estimate that company spending on R&D is allocated broadly one-third to discovery/pre-clinical and two-thirds to clinical, with roughly 35% of discovery/pre-clinical spending allocated to financing research with external

organisations. The key features of each of these, together with a definition of certain terms, are described in this chapter.

Figure 45: Typical process of research and development (small molecule) – stages and timing



Source: PhRMA Industry Profile 2012

Drug discovery

In the discovery phase, several hundred thousand chemical entities are typically screened for a pharmacological effect. This process may take two to five years, though new technologies help to significantly reduce the time required, not least high-throughput screening, combinatorial chemistry and an increasing knowledge of genomics.

The process of drug discovery begins with knowledge about the disease. This knowledge is generally developed through basic research conducted not only in the laboratories of pharmaceutical companies, but also in government, university and biotechnology company laboratories, and funded by the major pharmaceutical houses, charities and governmental agencies. Basic research reveals disease mechanisms or processes that become the targets of pharmaceutical intervention. It can be likened to the exploratory phase of scientific and drug research, where understanding of disease or functional pathways is sought and potential drug targets identified. Clearly, basic research in any scientific area is an ongoing event. However, exploratory work on specific drug targets generally averages 12 months.

Once the potential drug target is identified, the drug companies will attempt to develop a molecule that interacts with that target and which might form the basis of a drug. Techniques such as combinatorial chemistry come into play, as companies use rational drug design in an attempt to design a molecule which may interact with the identified target. Companies may also screen their chemical libraries as they seek potential drug candidates. If the objective is to target certain proteins, receptors or cells (vs. pathways), companies may attempt to produce hybridomas which manufacture

monoclonal antibodies against distinctive proteins on the target cell (e.g. HER2 in breast cancer). On average, companies may spend a year developing lead candidates. These early drug candidates will then be assessed using techniques such as high throughput screening (HTS) to determine the quality of the drug-target interaction. Molecular imaging is also used to try to assess drug interaction and the first in-vitro tests will be conducted to determine the drug's effect on animal cells (e.g. cellular levels of calcium, potassium), or human cells. Over two to three years, tens of thousands of molecules may be screened for a potential pharmacological effect, but only a handful may move forward for pre-clinical evaluation.

Combinatorial chemistry

Combinatorial chemistry is the synthesis of a substantial number of distinct compounds using similar reaction conditions. The process incorporates systematic molecular design, either by linking separate building blocks or by adding substituents to a core structure. As the process is fully automated or computerised, the 1,000-2,000 compounds required in order to identify three to four possible candidates can be screened in a matter of months. Many of the large international drug companies, as well as several smaller molecular design companies, have established extensive molecular libraries detailing the synthesis techniques, physicochemical properties and any experimental data, such as toxicology or pharmacokinetic studies. Overall, drug companies estimated that combinatorial chemistry has resulted in an 18-24 month reduction in the time taken to identify drug candidates.

High-throughput screening (HTS)

HTS utilises computer-controlled robotic systems for testing compounds systematically through a wide range of assays against an identified target receptor/protein. The compounds identified from combinatorial chemistry are bar coded, weighed and dissolved in a range of standard solutions and then screened using a wide range of assays. These include both the traditional assays and a wide range of new bacterial or human-cell assays, which provide a closer proxy for the conditions in the human body. Automated HTS has replaced what was previously a time-consuming and costly manual process and has contributed extensively to chemical information libraries.

Pre-clinical phase

Following these techniques, a handful of drug candidates are taken forward for pre-clinical testing in animals (in vivo or in the body) and further laboratory analysis (in vitro or outside the body), and the key pharmacological characteristics of a compound determined. These characteristics are summarised by the acronym ADMET, which stands for absorption, distribution, metabolism, excretion and toxicology. These determine the suitability of a new chemical to become a drug. If a compound appears to have important biological activity and may be useful as a drug, tests evaluating the ADMET criteria are conducted on the major organ systems (such as CNS, cardiovascular and respiratory systems). Other organ systems are evaluated when potential problems appear. These pharmacology studies are conducted in animals to ensure that a drug is safe to be tested in humans.

An important goal of these pre-clinical animal studies is to characterise any relationship between increased drug doses and toxic effects. Drug development will be halted if tests suggest that a significant risk may be posed in humans, especially organ damage, genetic defects, birth defects and cancer. On average, drug candidates spend one to two years in the pre-clinical stage.

Clinical trials in humans

A drug sponsor may begin clinical studies in humans once the FDA is satisfied that the pre-clinical animal data do not show an unacceptable safety risk to humans. The pharmaceutical company will file an investigational new drug (IND) application with the regulatory authorities. Once approved, human trials can begin, although at all stages, sponsors and investigators must follow regulations designed to ensure safety. Indeed, for US applications, an Institutional Review Board must review and approve a research plan before the trial begins and thereafter continuously monitor the clinical process.

There are four main phases of clinical trials in drug development, and a new drug application, or NDA, typically involves almost 70 clinical trials involving more than 4,000 patients. The definitions are functional and drug development candidates need not necessarily pass through one phase before the next is undertaken; that is, clinical trials may overlap. Equally, it is important to appreciate that a drug may be in different phases of the trial process for different indications. In other words, a drug may be approved for use in hypertension, but still be going through the clinical development process for congestive heart failure.

Phase I trials

Phase I trials represent initial safety trials on a new medicine. They are usually conducted in a small number of healthy male volunteers and are undertaken to establish the dose range tolerated by volunteers, as well as to gain further knowledge of the pharmacokinetics of the drug in humans. In the case of drugs for the treatment of life-threatening diseases, such as cancer, Phase I trials are usually conducted in ill patients, rather than healthy volunteers. Trials typically involve 20-100 patients and account for less than 10% of total R&D spending. Typically, around 40-50% of Phase I drug candidates fall by the wayside.

Phase II trials

Phase II trials are conducted to evaluate efficacy and safety in selected populations of patients with the disease or condition to be treated or prevented. Objectives typically focus on dose response and dosing frequency, together with safety, efficacy and side effect characteristics. Trials typically involve 100-500 patients and fewer than 50% of Phase II drug candidates will progress to Phase III. In total, we estimate Phase II trials account for around 10-15% of R&D budgets. Note that a Phase IIb trial is typically a larger and more rigorous demonstration of a medicine's efficacy, while a Phase IIa study can be thought of as a proof of concept study (i.e. the trial is seeking to demonstrate that the concept works).

Phase III trials

Phase III trials are typically conducted once the efficacy of a medicine has been demonstrated and the optimal dose range determined. These are also conducted in patients for whom the medicine is intended and are designed to demonstrate safety and efficacy in larger patient populations. Several trials may be conducted, as the sponsor of the trials seeks to demonstrate the benefit of the drug against placebo, in combination with other treatments or relative to an existing treatment. The number of patients involved will depend on the disease for which the drug is intended. A cancer drug may only be investigated in a few hundred patients, while a drug for hypertension would be studied in several thousand. Key to determining the required number of patients is the need to differentiate the drug from placebo/competitor on statistical analysis, as well as to identify potentially rare side effects. A drug will not gain approval unless it has shown statistically significant superiority over placebo in clinical trials. Phase III trials are often described as pivotal trials, and typically form the major part of

the submission to the regulatory authorities. Phase III trials are estimated to account for over 35% of a company's R&D spending.

Phase IV or post-marketing surveillance

Assuming the successful completion of at least two pivotal trials, the drug sponsor submits a new drug application (NDA) to the relevant regulatory authority, such as the FDA in the US, the EMA in Europe or the MHLW in Japan, for approval to manufacture, distribute and market the drug. However, the clinical process does not end with the approval of a drug. Sponsors are required to undertake post-marketing surveillance to monitor a drug's safety, a process that continues for the marketing life of the drug. The objective of such surveillance is to monitor for unexpected side effects. Statistically, adverse reactions that occur in fewer than one in 3,000-5,000 patients are unlikely to have been detected during the clinical process and may be unknown at the time of a drug's launch. Thus, rare adverse events are more likely to be detected once the drug has exposure to a substantial patient population. Should serious adverse events occur anywhere in the world, the pharmaceutical companies must inform the regulatory agencies within 15 days. Depending upon the frequency and severity of the adverse event, changes to a drug's labelling (as was the case with Biogen Idec's Tysabri) or indeed its complete withdrawal (as happened with Merck's Vioxx) may be deemed necessary.

Ongoing studies

It is important to appreciate that almost all companies will continue to undertake clinical trials on launched drugs and to use the data gathered to strengthen the drug label. This may be done to develop further long-term data on the efficacy/safety of the treatment or seek approval for additional indications, e.g., anti-depressant treatments may also be used to treat other anxiety-related indications (social phobia, obsessive compulsive disorder, etc). Equally, companies may undertake trials to demonstrate the greater efficacy or side effect profile of the drug relative to a class competitor and so strengthen the drug's marketing message and appeal to physicians.

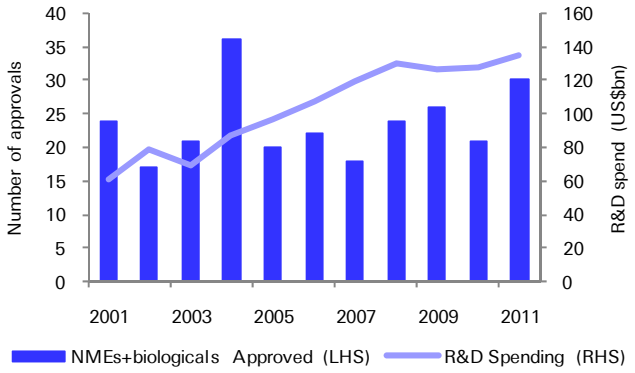
R&D productivity

The global pharma is in the process of absorbing >$100 billion of patent losses over 2012-2016. Although we believe a number of companies are sufficiently prepared to make this hit a dip rather than a sustained slump in earnings, the industry's ability to replace lost sales through pipeline development is one of the greatest debates amongst investors in the sector. These concerns reflect that industry approvals have (at best) stagnated over the last ten years, while global industry R&D costs have escalated.

The global pharmaceutical industry spent a cumulative $1,136 billion in R&D over 2000-2011, yielding 259 NME and biologic approvals. However this return is perceived as disappointing by many investors. We calculate that European large-cap pharmaceutical companies currently continue to make returns well in excess of our estimated industry cost of capital (we assume a 9% WACC). To a significant extent this reflects durability of tail end products and continued excess returns on R&D investments made during the 1990's. As an example, close to 90% of GSK's pharmaceuticals sales come from drugs launched a decade or more ago and around a third of its profits are generated from a single drug, combination asthma/COPD treatment Advair, launched in 2001. Given the level of ongoing patent exposure along with escalating R&D costs and at best stagnant new approvals, the industry's ability to maintain returns on R&D spend is a major point of debate.

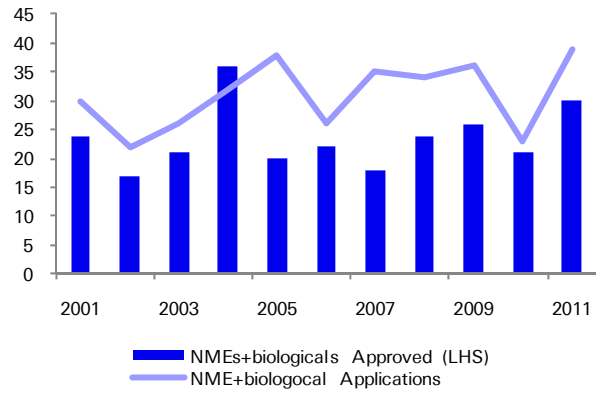
In view of increased pressure on top-line growth, patent expiries and the determination of payers to control the increase in expenditure on medicines, pharmaceutical companies have been focusing on controlling the cost base, especially R&D expenditure. Most companies now have a committee overseeing the firm's R&D efforts, choosing to focus on molecules that have the highest potential of eventually being approved. A drug's prospects are routinely reviewed during each clinical phase as data becomes available, and the committee makes a decision whether to continue or stop the trial. As seen in Figure 46 and Figure 47, the number of NME approvals has not kept pace with the growth in R&D expenditure for the industry, although the FDA's NME approval ratio does not exhibit a decline.

Figure 46: FDA NME approvals vs industry R&D expense



Source: Deutsche Bank
Includes biological from 2004

Figure 47: FDA NME applications vs approvals



Source: Deutsche Bank
Includes biological from 2004

A significant element of the decline in product successes can be attributed to several factors. Among other things, these likely include more safety-conscious regulatory bodies, crowded therapeutic classes requiring products to be better differentiated, a greater risk of drug-drug interactions and the greater complexity of today's molecules.

However, with today's pharmacopoeia already encompassing many very successful treatments, the bar for success is far higher than ever before. Therefore, companies have begun shifting the focus of their research to address more severe and unmet needs. Hence, there are signs that this drought may be coming to an end.

Analysis of R&D pipelines

Given that a significant proportion of a pharmaceutical company's market capitalisation is accounted for by the value of its R&D pipeline, it is not surprising that a major part of pharmaceutical analysis focuses on assessing the potential of drugs in development. This is not an exact science and is probably the area of pharmaceutical analysis most prone to debate.

Until recently, pipeline analysis could be summed up as 'spot the blockbuster' and focused on identifying high-potential drugs (potentially able to achieve over a billion in sales) in development. Most excitingly, these are drugs with a totally novel mechanism of action, targeted at a disease with large patient numbers, or where there is a high level of unmet medical need. In addition, many blockbuster drugs have also come from established drug categories, where substantial sales have been won by offering modest improvements over existing products.

As pharmaceutical companies get bigger, however, the scope for one blockbuster drug to exert significant earnings leverage clearly diminishes. As a result, factors such as R&D productivity and risk-reward balance are becoming increasingly important.

R&D productivity

The historical average for pharmaceutical industry R&D productivity has been just over one NCE (new chemical entity) launch per year. Large companies now target at least two to three NCE launches per annum, though most have not have achieved this in recent years. A crude measure of R&D productivity can be gauged by looking at the number of drugs in development in light of their projected launch date, though we must be cognizant that the risk of failure increases significantly in earlier phases of development.

Risk-reward

Ideally, an R&D pipeline should have a good balance between innovative products with high market potential but possibly a higher-than-average chance of failure, and products that act by established mechanisms of action (often called 'me-too' drugs), where the chance of failure is reduced but where market potential may be limited due to existing competition. A company whose entire pipeline is built on innovative mechanisms is at significant risk of bringing nothing to market, though the rewards may be greater if successful. In recent years, regulators have increasingly looked to encourage innovation by creating higher hurdles for me-too products.

Distribution

To ensure a steady flow of new drugs to the market, a company should ideally have drugs in all stages of clinical trials. The optimal structure is pyramidal, with more drugs in Phase I than in Phase II and more drugs in Phase II than Phase III. This reflects the risk of new drug failure at each stage of the process, which is currently estimated by industry consultants at 8 out of 10 in Phase I, 7 out of 10 in Phase II and 2-3 out of 10 in Phase III. As discussed above, the more innovative the product, the higher the risk of failure. Not surprisingly, a company with a 'pipeline gap', with few products in Phase III trials, is a cause for concern, as it may suggest a higher-than-average rate of new drug failure and limited long-term growth, and/or the need to spend cash to in-license or buy products.

Pipeline potential

In assessing the value of an R&D pipeline, analysis usually begins with an estimate of peak sales for each product. In most instances, this usually represents forecast annual sales around five years from launch. For a drug intended for use in a disease where there is already a well-established market, estimated potential is most likely to be based on a target market share. This would obviously reflect potential advantages of the new drug over the competition, but should also take into account the marketing strength of the originating company. For a drug targeted at a disease for which there is little or no existing competition, market potential would be estimated through first principles in terms of patient numbers, likely penetration rate and estimated price. In general, smaller patient numbers and more severe diseases have been associated with a higher drug price. In addition, drugs predominantly prescribed by hospital doctors would tend to require less marketing cost than those targeted at a primary-care audience. When estimating the potential future sales contribution for a company's pipeline products, one common method is risk-adjusting future sales to reflect the risk of failure to bring the drug to market.

Research glossary

So, you have decided to try reading a clinical trial. What do these terms mean? Here's a brief explanation to some terms you are likely to encounter:

Placebo: An inactive agent or 'sugar pill' given to the trial candidate in place of the active drug.

Double blinded: Neither patient nor physician is aware which of the patient groups is receiving the placebo and which is receiving the active drug.

Single blinded: The patient is unaware but the physician is aware which patient is receiving a placebo and which is receiving the active drug.

Open (unblinded) trial: Both patient and physician know who is taking drug (or not).

Control: The reference arm of a clinical trial. It may use a placebo or, in some cases, a reference drug already approved and widely used for the relevant indication.

Cross-over: The patient groups alternate treatment through the course of the trial, that is, one half would take the active drug and the other placebo/control, and at a set time, both groups swap or cross over.

Randomised: Each patient enrolled in a trial has an equal likelihood of being assigned to any given treatment arm regardless of their gender, race, age, disease status, etc.

Intention to treat: Every patient initially involved in the trial is registered in the final analysis, including those who withdrew for any reason. This is considered a more robust analysis than 'as treated'.

As treated/per protocol: Only patients who completed treatment are included in the final analysis of clinical data.

Primary end-point: The primary and most important objective of the study, on which the success of the study will usually be determined.

Secondary end-point: Other objectives of the study which are not the key measurement.

p-Values: A statistician's term, measuring whether an outcome is statistically significant. The lower the p-value, the greater the significance. A p-value of $p>0.05$ suggests limited statistical significance, while $p<0.01$ is considered highly significant. A $p<0.05$ is typically the benchmark for success or failure.

Non-statistically significant: Insignificant result, usually taken as $p>0.05$ or a 95% confidence level.

Patient arms: Trials often allocate each patient to one of several groups, each receiving a different treatment, e.g. different dose, different regiment.

Genomics and biotechnology

Genomics

We have all heard of DNA and genes. In a nutshell, these are codes that when read, tell a cell in the body to produce a protein which has a function – eg. sends a message, produces an antibody, tells the cell to grow and divide, etc. By understanding the genome (the body's collection of genes), we can better understand disease, and hopefully treat it. The sequencing of the human genome potentially heralds the start of an era of great opportunity and offers the drugs industry the opportunity of better understanding the body's workings and basis of disease, together with the potential for an unprecedented increase in drug targets. With an increased understanding of the human genetic code and the roles of molecules which they encode, drug companies have been able to rationally design new drugs specific to new receptor targets, allowing the tailoring of medicine to an individual's specific disease.

The genome

Genomics is the study of the genome (the entire set of genes within a human). It contains instructions for the production of the multitude of molecules which govern cell chemical activity. Our genetic code is comprised of a specific sequence of molecules called deoxyribonucleic acid (DNA), which are organized in a double helix structure, comprising two intertwining and complementary strands of genetic instructions.

Deoxyribonucleic acid (DNA)

Each DNA strand consists of a linear arrangement of linked sub-units called nucleotides. These nucleotides may be one of four different molecules (known as nitrogenous bases), which are called adenine (A), thymine (T), cytosine (C) and guanine (G). Though there are only four types of nucleotides, it is their sequence on the DNA strand which determines the protein to be produced. Each base on one strand of DNA is linked to a specific base on its complementary strand, forming base pairs. Importantly, strict rules are adhered to, such that A always bonds with T, and C with G. The limited number of bases and fixed nature of pairing hugely reduces the scope for error, yet the potentially limitless permutations of bases in the DNA sequence maximises diversity. In total, the human genome comprises roughly 3.1 billion base pairs.

Chromosomes

Within the human cell nucleus, DNA strands are distributed across 23 pairs of chromosomes (46 in total). Arranged linearly along these are an estimated 100,000 genes. A gene is a specific sequence of nucleotides which direct protein synthesis. They may vary widely in length. Interspersed within and around them on the DNA strand, are 'junk regions' that have no known coding function. Interestingly, of the 3.1 billion base pairs, only 10% are thought to contain genes.

Polymorphisms

Even though we each have 23 pairs of chromosomes, the exact make-up of our individual DNA is not identical. Minor variations in our genes exist, and it is these differences which are responsible for our individuality. If all of our DNA were identical, then we too would all be identical – one huge family of clones, indistinguishable from one another. These minor variations in genes are known as polymorphisms (many forms). They are often benign, but some variations are associated with a higher risk of

disease. For example, as a result of polymorphisms, some people may be more likely to develop diabetes or Alzheimer's disease or certain cancers. Equally, differences in our genetic make-up may determine whether we react poorly to a particular drug. Because most polymorphisms involve only a change in one nucleotide on the DNA strand, they are often referred to as single nucleotide polymorphisms (SNPs or 'snips'). Those subsets of individuals who have a similar SNP are said to be of the same genotype (i.e. genetic type).

Gene expression

Genes do not act independently. Rather, so-called control regions, which are specific sequences outside of the gene, act to turn a gene on or off, and hence, determine the nature of the cell's activity. This allows for functional differentiation between cells, despite the fact that each cell has an identical genetic code. Thus, a liver cell produces liver enzymes, while a pancreatic cell produces molecules specific to the pancreas, and so on. The term 'gene expression' refers to whether a gene is turned on (expressed).

The process by which a gene synthesises a single protein (gene expression) is based on interpretation of the sequence of its base pairs. Every three base pairs along the gene is called a codon, and each codon codes for one of 20 particular amino acids; the number and order of codons along a gene sequence determines the specific amino acid sequence that makes up a protein chain. Thus, codons are akin to instructions for words, which are ordered together along a gene to make up a sentence (the protein). However, to continue the analogy, inserting the punctuation marks is often dependent upon instructions from other genes. This all adds to a complication of understanding of how our genetic code directs the myriad of cellular processes.

Transcription

In order for codons to be read and proteins formed, the gene's coiled DNA strands must unwind and serve as a template. Within the cell nucleus a complementary strand of what is called the mRNA (messenger ribonucleic acid) is produced, using the DNA template. This process is known as transcription. The transcribed mRNA sequence is a near mirror image of the original DNA, except that a nucleotide called uracil (U) takes the place of thymine (T). The mRNA strand then moves out of the cell's nucleus and into the surrounding fluid or cytoplasm. Here it attaches to a cellular constituent, a ribosome, and is translated (the ribosome reading the mRNA) into a sequence of amino acids. This chain of amino acids (aka protein) is then either immediately functional or undergoes further modification within the cell to gain its functionality.

The Human Genome Project

The genomics revolution began with the Human Genome Project in 1990, which aimed to sequence the entire human DNA. The enormous task of sequencing the over 3.1 billion base pairs of genetic code was the result of collaboration by academic institutions and research centres around the world, and was eventually completed in 2003. However, knowing the sequence of the human genome is only the first step along a very long road towards understanding the basic make-up of our chemistry. To date, we know the sequence of the 3.1 billion base pairs, but little about what they encode for and where the different coding sequences, or genes, are located. Equally, we have only limited knowledge of how different genes interact. Even more bewilderingly, genes encode for proteins, and it is these proteins that are the main mediators of function in both diseased and healthy pathways. Thus, if we are truly to benefit from our understanding of genes, we must understand the actions of the million-plus proteins encoded by our DNA. Indeed, for the pharmaceutical industry, it is the proteins that represent the most likely drug targets. Consequently, the study and

understanding of proteins (termed proteomics) will likely be the key to delivering value and drugs from our knowledge of the human genome and its workings.

Pharmacogenomics

Pharmacogenomics is the study of genotypes and their relationship to drug action. It is about using the right drug on the right person, and explains why some patients react favourably to drug treatment and others adversely, the answer to which is increasingly believed to be genetic. For example, a drug such as Roche/Genentech's cancer treatment, Herceptin, is only directed at cancer cells which express the HER2 gene and receptor. This presents a potential opportunity for companies which are able to develop diagnostic tests.

Biotechnology

Biotechnology is, in essence, man's use of the cells' chemistry to produce therapeutically useful proteins. In large part, biotechnology seeks to industrialise and manipulate chemical reactions that occur at the cellular level and produce significant quantities of structurally complex molecules.

The use of biotechnology is not new. For thousands of years, man has taken advantage of the chemistry of micro-organisms to produce desirable products. For example, at its simplest level, the process of alcohol production using yeast represents an example of using biotechnology on an industrial scale. However, in this guide, we use the term 'biotechnology' to describe protein-based drugs in the general sense.

Monoclonal antibodies (mAbs)

From a pharmacological perspective, the biotech industry took off in the late 1970s and early 1980s as scientists developed techniques to isolate genes which encoded for specific proteins and insert them into the genetic material (DNA) of cells that divided rapidly whilst producing the desired protein. In so doing, a protein could, in theory, be produced in commercial quantities.

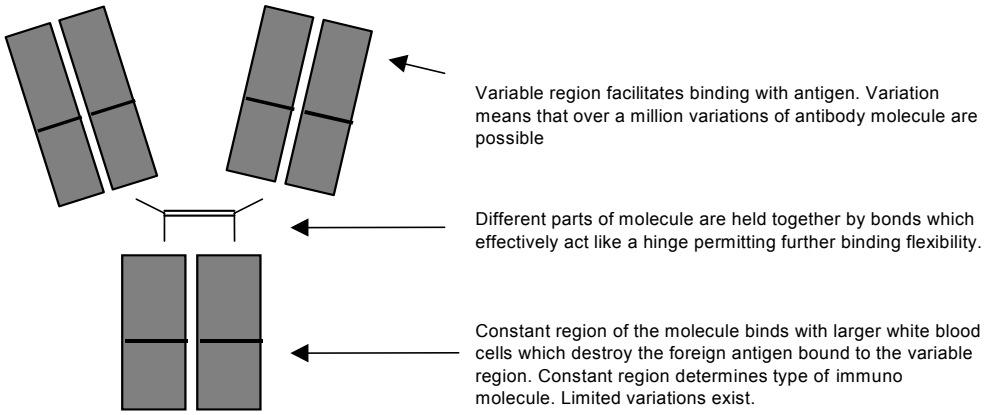
Most significant was the discovery by Kohler and Milstein in 1975 that by fusing an antibody-producing white blood cell (or B lymphocyte) with a mouse-derived cancer cell, a hybrid cell (hybridoma) capable of mass production of a single specific antibody (a monoclonal antibody or mAb) was possible. (An antibody is a protein that is created by the host's immune system in response to a foreign particle called an antigen). This was seen to have particular relevance in the treatment of cancer, but also other ailments where a specific protein could be targeted. The theory was simple. If antibodies specific to certain types of cancer cells could be produced in commercial quantities, then target-specific drugs could be developed. This could then be administered to the cancer patient and would kill the cancer cells to which the antibodies attached, while leaving healthy cells intact.

Diversity

Humans' ability to produce a diversity of antibodies lies at the heart of the immune system. In order to fully appreciate the possibilities of antibody technology itself and some of the products in development, it is useful to have a basic understanding of the structure of an antibody. Antibodies take the form of a pincer-shaped molecule comprising four main regions (Figure 48). The constant regions determine the function of the antibody (e.g. whether it is raised in response to a parasite or an allergen) and facilitate binding with white blood cells of the immune system that ultimately destroy the foreign antigen. The variable region is the part that effectively adheres to the antigen, and is so named because the tremendous variation observed in this region.

Antibody genes are inherited as fragments that can rearrange to form the genes encoding antibodies to a variety of antigens. Mammals have been observed to produce over 100 million antibody variations. As so many variations are possible, given time, the body's immune system can theoretically develop antibodies to almost any disease. Once an antibody is created, it is mass-produced by the body until the pathogen is destroyed.

Figure 48: Simplified structure of an antibody molecule

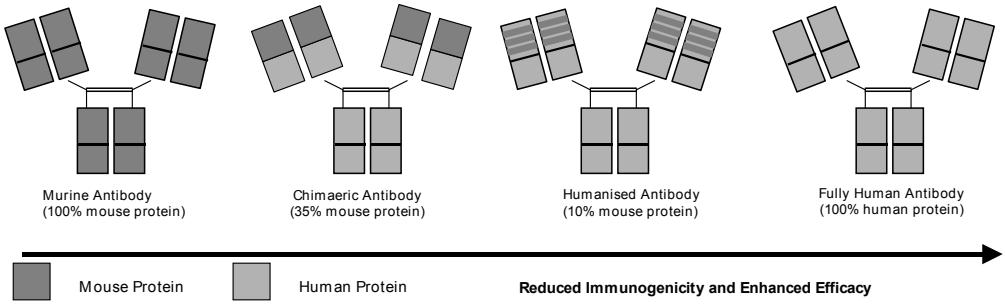


Source: Deutsche Bank

Therapeutic use

From a commercial viewpoint, production of effective monoclonal antibodies has proven very challenging. As it is difficult to get a human immune cell to produce antibodies against human proteins, initial work in monoclonal antibodies was done with mice cells (hence, murine in origin). Once sufficient quantities of antibodies were produced against the target protein, they could then be injected into humans. One obstacle was immediately apparent – murine (mouse derived) proteins are foreign to humans and elicit an unwanted immune response to the antibody itself. They are then destroyed before they are able to achieve their effect. In an attempt to overcome this, scientists were able to replace the constant portion of the murine antibody with a human version of it, resulting in a chimeric antibody. Over the years, scientists have progressively reduced the murine portion of the monoclonal antibody. For example, humanized antibodies are largely identical to human antibodies, with only some portions of the variable fragment retaining their non-human origin. With the advent of new technologies, scientists are now able to produce antibodies which are fully human (Figure 49). The WHO's International Nonproprietary Name (INN) working group has developed a nomenclature for naming monoclonal antibodies, based on the target or disease and the source (Figure 50).

Figure 49: Range of antibodies from 100% mouse to 100% humanised



Source: Deutsche Bank, EvaluatePharma

Figure 50: INN nomenclature of monoclonal antibodies

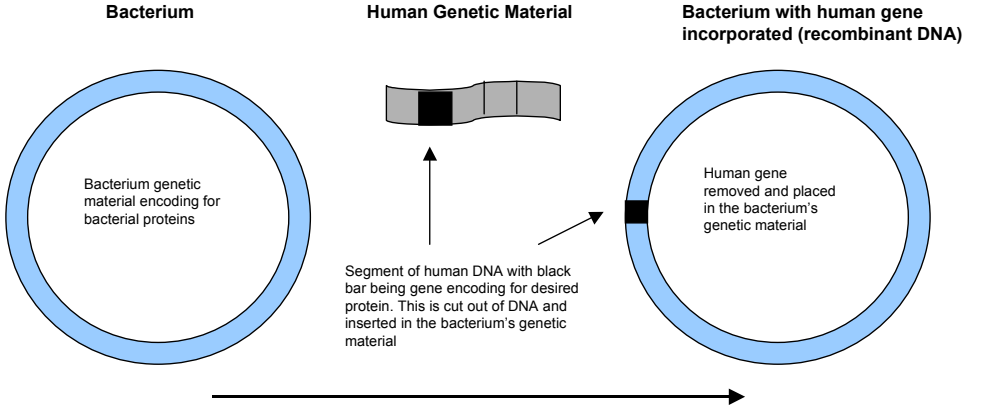
Substem A		Substem B	
Name	Target	Name	Origin
- b(a) -	bacterial	a	rat
- c(i) -	cardiovascular	axo (pre-substem)	rat/mouse
- f(u) -	fungal	e	hamster
- k(i) -	interleukin	i	primate
- l(i) -	Immune-modulating	o	mouse
- n(e) -*	neural	u	human
- s(o) -	bone	xi	chimeric
- tox(a)	toxin	-xizu-	chimeric/humanized
- t(u) -	tumour	zu	humanized
- v(i) -	viral		

**under discussion*
Common suffix for monoclonal antibodies is -mab
Name = prefix + substem A + substem B + suffix
Source: World Health Organization, Programme on International Nonproprietary Names (INN)

Recombinant technology

Beyond the use of biotechnology to produce molecule-specific drugs, biotechnology also finds an important application in the production of essential human proteins, for example, insulin and blood-clotting activators, Factors VII and VIII. The concept here is simply to discover the gene responsible for the production of the particular protein and to insert that gene (recombine it) in rapidly dividing cells, typically a bacterium or yeast cell of some kind. The cells would then produce the relevant protein (e.g. insulin) which could be extracted, purified and used for therapeutic purposes to replace the patient's missing or dysfunctional proteins.

Figure 51: Recombinant theory



Simplified diagram illustrating basics of recombinant technology whereby a desired gene which codes for a specific protein is cut from the genetic material of one organism (say man) and inserted in the genetic material of a rapidly dividing cell. By combining the desired protein encoding gene in the genetic material of a rapidly replicating simple organism the relevant protein can be mass produced.

Source: Deutsche Bank

Regulation

The regulatory process

To date, regulators globally have not created a single harmonised protocol for drug approval. As such, separate regulatory bodies and approval processes exist in each of the major markets of the US, Europe and Japan. While future harmonisation is an objective (and a process, with this as an aim, at the International Conference for Harmonisation, or ICH, is ongoing), as things stand today, a new drug needs to go through at least three separate approval processes if it is to be launched in the world's three largest markets. This is clearly both costly and time consuming. The requirements of the different regulators also mean that companies frequently undertake further clinical trials in order to meet the regulatory needs of the authorities in the different territories, a feature which further increases the already substantial costs surrounding the regulatory process. Having said this, the actual filing requirements across the different regulatory regimes discussed here are gradually converging. However, one major difference between attaining marketing approval in the US as compared to other countries is the need to agree on pricing with the authorities in both Japan and Europe. This often leads to delays between approval and product launch.

Regulation in the US

The FDA

As with drug development, the process of regulatory approval in the US falls under the supervision of the Food & Drug Administration (FDA), specifically the Centre for Drug Evaluation and Research (CDER). Following a pre-submission meeting, a new drug sponsor (usually the drug manufacturer) will submit a file, called a New Drug Application (NDA), for a new chemical entity (NCE) to the FDA for approval to manufacture, distribute and market the drug in the US, based on the data collated through the clinical trial process. This file comprises a multitude of information, including written reports of each individual study, manufacturing data and a summary of all available information received from any source concerning the safety and efficacy of the drug. Included in this must usually be at least two pivotal trials that represent the key clinical trials confirming efficacy for any NCE submission. At least one of these trials must have been either undertaken in the US or have been conducted in a group with at least 20% of patients from the US, such that the results can be extrapolated to the US population. In addition, 120 days prior to a drug's anticipated approval, the sponsor must provide the FDA with a summary of all safety information surrounding the new drug, including any additional safety data obtained from trials undertaken during review.

Advisory committees

Following NDA submission, the FDA has 60 days to inform the sponsor that the application is complete and worthy of review. At this stage, the FDA designates the review track for the product. Effective October 2012, the standard review process is ten months from date of filing (or twelve months from date of submission), but in cases of a therapeutic breakthrough, a drug may be granted a priority review, which must be completed within six months from date of filing (or eight months from date of submission). Assuming FDA acceptance, depending on the therapeutic focus of the drug, the submitted NDA will then be forwarded to an appropriate specialist department. For example, a cancer treatment may be forwarded to the Division of

Oncology and so on. The FDA also frequently seeks advice from advisory committees on drugs, particularly on all NCEs and major new filings. These comprise independent scientific experts, physician researchers and statisticians who will make a recommendation to the FDA as to whether an NDA should be approved. The FDA is not obliged to but will frequently follow their recommendation.

Complete response letter

Assuming that the NDA meets the efficacy and safety requirements of the FDA, if there are no outstanding issues, a drug may be granted an immediate approval at the end of the formal review process. However, since 2008, if there are labelling issues, or if the FDA has outstanding concerns, it will issue a 'Complete Response' letter, detailing deficiencies in the drug application and actions necessary for approval. This replaces the earlier process where the FDA issued an "Approvable Letter" (meaning the drug is 'basically approvable if certain issues are resolved') or "Not Approvable Letter" (meaning the drug cannot be approved for certain reasons).

Following a complete response letter, the company may respond in one of three ways – 1) withdraw the application, 2) request a hearing, or 3) resubmit the application. A failure to resubmit or request for an extension within a year is taken as a withdrawal of the application.

Resubmissions following a complete response letter may be divided into two categories. A 'Class 1 resubmission' contains complete information regarding the final form of the drug, as well as some minor new analysis of previously submitted data or minor new information. The review period for this will be two months from date of receipt. A 'Class 2 resubmission', which is a catch-all for all other resubmissions, has a review period of six months from date of receipt.

Drug label and black boxes

A drug label represents the information that must be made available to consumers whenever the drug is dispensed (prescribing information on the sheet of paper enclosed in the packaging with each drug). Importantly, the label details all the safety data, together with any specific marketing or superiority claims permitted by the FDA (in other words, claims made following clinical trials that demonstrate the drug's superior efficacy relative to other products). In certain instances, the FDA may require that the label emphasize potential drug side effects, that is, a health warning. This might be by way of bold text or, in extreme cases (and typically if the drug can result in fatalities), the addition of a warning in a clearly visible black box. This is entitled a Black Box Warning and is clearly not conducive to sales, albeit many drugs now have these and their effect is perhaps reduced by their frequency.

The label is important to the drug company, as it determines the claims about the product which can be made during marketing. Promotional claims cannot be made unless they are included in the drug's label.

Risk Evaluation and Mitigation Strategies (REMS)

For certain drugs that have a known or potential safety risk, if it has demonstrated a clear benefit in a certain group of patients, the FDA may approve the drug with the proviso that the company implement an approved Risk Evaluation and Mitigation Strategy (REMS). The REMS puts in place guidelines to ensure that the drug is prescribed to the group where the benefits outweigh the risks, and may take the form of any or all of the following: a Medication Guide, a Patient Package Insert, a communication plan to healthcare providers (of the risks) and/or a system to assure safe use. It must also contain details of a system of implementation and a timetable for

assessment of the REMS' effectiveness. A drug company may submit a proposed REMS voluntarily, without being required to do so, or the FDA may later require a REMS for an approved drug following new safety data from post-marketing surveillance.

ANDAs and efficacy supplements

Outside of new drug applications (and the INDs discussed in the Research & Development section of this report), the FDA also frequently reviews two other types of drug applications – abbreviated new drug applications (or ANDAs) and efficacy supplements.

- **ANDAs:** An ANDA is the submission required for launch of a generic version of an existing approved drug. They are called abbreviated as they are not required to include data from animal and human clinical studies. Instead, they must demonstrate that the generic drug is bioequivalent to the innovator drug. This means that the generic drug must prove that it is chemically identical to the branded product and is absorbed and metabolized by the patient in the same way, such that the blood concentration profile of the both products are identical.
- **Efficacy supplements:** Efficacy supplements are filed for drugs which are already approved, but for which a new/additional indication is being sought (e.g. the use of the anti-depressant Prozac for treatment of panic disorders). Depending on the indication, the drug company may or may not be required to submit clinical data demonstrating efficacy in this additional indication, together with additional safety data. The timeframe for approval is six months for priority efficacy supplements, or 10 months for standard efficacy supplements.

Prescription Drug User Fee Act (PDUFA)

Reform of the FDA over the past decade has seen a vast improvement in the time taken for regulatory approval. This process began with the first Prescription Drug User Fee Act (PDUFA) in 1992. Of note, this Act (and each subsequent Act) contains a 'sunset provision' for automatic expiration every five years, when they have to be renewed. Each subsequent Act has also taken the nomenclature PDUFA II, PDUFA III, accordingly. In this way, Congress introduced greater flexibility to the act by enabling issues arising in the existing legislation to be tackled and funding requirements assessed following a reasonable time period.

- The 1992 Prescription Drug User Fee Act (PDUFA), under which the pharmaceutical industry agreed to pay application fees at the time of submission of a New Drug Application to enable the FDA to hire additional reviewers, and facilitate the drug approval process. In return, the FDA committed itself to a target of responding to 90% of standard reviews within 12 months, and 90% of priority reviews within six months.
- The 1997 FDA Modernisation Act (FDAMA or PDUFA II) raised the bar for review times and set out goals with the aim of improving communication between the FDA and drug companies. In return for increased fees, the FDA agreed to review 90% of standard ANDAs within 10 months, from the prior target of 12 months. It also set out timeframes in which the FDA was to have formal meetings during the drug development phase to review the data and address issues.
- The 2002 Public Health Security and Bioterrorism Preparedness and Response Act (which included PDUFA III) allowed the FDA to use fees to improve

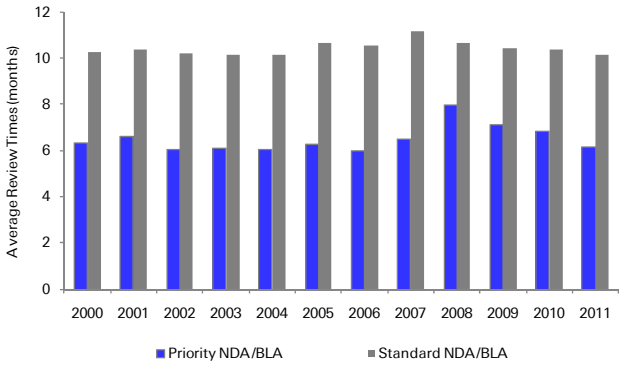
pharmacovigilance and post-market risk management, and included guidance on good review management and practices (GRMPs). On a related note, 2002 also saw the passage of the Medical Device User Fee and Modernization Act (MDUFMA), which extended the collection of application fees to the approval process for medical devices.

- The 2007 FDA Amendments Act (FDAAA or PDUFA IV) included amendments to increase fees (totalling c.275 billion from 2008-13) to facilitate the approval process and to cover costs associated with a new initiative focusing on drug safety, which includes the implementation of REMS for drugs, post-approval marketing surveillance and monitoring of direct-to-consumer advertising.
- The 2012 Food and Drug Administration Safety and Innovation Act (FDASIA) included PDUFA V and introduced GDUFA and BSUFA. PDUFA V modified the FDA review process goals to be effective from date of filing, vis-à-vis from date of submission under PDUFA IV, effectively increasing the length of the review process by two months. PDUFA V also committed to greater focus on orphan drugs and on biomarkers and pharmacogenomics, through developing dedicated staffing and training. The Act introduced two new forms of user fees: Generic Drug User Fee Act (GDUFA) and the Biosimilar User Fee Act (BSUFA). The expected revenue for FY13 is about $700m and $300m from PDUFA and GDUFA, respectively.

User fee deadlines and priority reviews

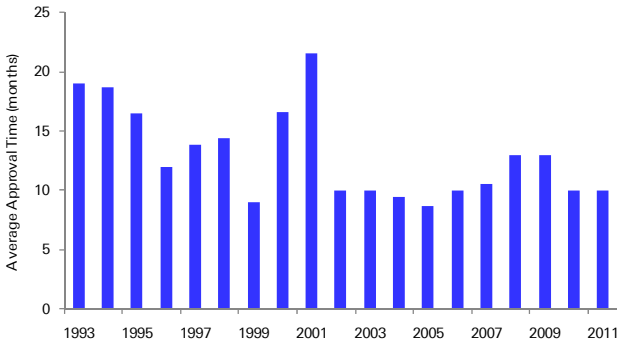
Since PDUFA II, the FDA has committed itself to respond to 90% of all standard reviews within ten months. Failure to do so means that the FDA is obliged to return the user fee to the drug sponsor (2012 set at $1.84 million for NDAs with clinical data, $920,000 if no clinical data or efficacy supplements). Note that the FDA is only obliged to issue a complete response letter within this time period. The time to final approval may, as previously indicated, take longer if the labelling discussions are protracted, or if the FDA requests additional data.

Figure 52: FDA average review time - NDA/BLA



Source: US Government Accountability Office

Figure 53: FDA average approval time –NME/NBE



Source: US Food and Drug Administration

Fast Track, Accelerated Approval and Priority Review

- **Fast Track**: This is a process by which the FDA expedites the development and approval of a drug that 'whether alone or in combination with one or more drugs, is intended for the treatment of a serious or life-threatening disease or condition' and fills an unmet medical need. To show that it addresses an unmet medical need, there is either no treatment for that particular disease or the drug provides a potentially superior treatment compared with what is currently

available for the disease. This may take the form of superior efficacy, less serious side effects, or decreased clinical toxicity compared to current treatment. A drug granted fast-track status may receive some or all of the following benefits – more frequent interaction and feedback from the FDA during the drug development process, eligibility for Accelerated Approval, Rolling Review (where a drug company may submit completed sections of the NDA for FDA review, rather than waiting for the entire application to be completed), and eligibility for Priority Review.

- **Accelerated Approval**: Where the Fast Track process facilitates drug development, the Accelerated Approval process allows for an earlier approval of drugs which treat serious diseases and address an unmet medical need. Understanding that clinical outcomes may occasionally require years of observation, for accelerated approvals, a surrogate end-point is used as a measurement of outcome. This may take the form of a laboratory measurement (e.g. serum cholesterol levels), clinical signs, or imaging studies. Though this may shorten the time required to collect sufficient data for approval, post-marketing clinical trials (also called Phase IV confirmatory trials) will be required to ensure the drug demonstrates the anticipated benefit. The FDA will review the drug again at a later date, where full approval of the drug will rest on the results of the Phase IV trials. Failure to gain full approval at this time may result in the drug being withdrawn from the market.
- **Priority Review**: Where a Standard Review is used for drugs which offer minor benefits compared to existing therapies, a Priority Review is granted for drugs which offer a major advance in treatment or address an unmet need. This is not necessarily restricted to serious illnesses. Since the PDUFA in 1992, the FDA has committed to complete 90% Priority Reviews within six months. Following a request for a Priority Review by the drug company, the FDA will determine the appropriate review status and respond within 45 days.
- **Breakthrough therapies**: This is a new designation created under FDASIA (PDUFA V), to reduce time for development and review of drugs that treat serious or life threatening disease, where preliminary data from clinical trials shows substantial improvement over existing drugs. FDA is required to decide if a therapy qualifies as 'breakthrough' within 60 days of application and if the designation is granted, expedite development and review through sponsor meetings, development advice, involving review staff to ensure efficient review and ensuring appropriate trial design.

Regulation in the EU

Until the mid-1990s, the medical committees of the individual European states determined regulatory approvals in European markets. Limited harmonisation existed and approval of a single medicine across Europe was often time-consuming and costly. However, in 1995, a new European system for the authorisation of medicinal products came into operation with the foundation of the European Agency for the Evaluation of Medicinal Products, later shortened to European Medicines Agency (EMA).

EMA

The EMA's main role is to coordinate and manage the drug approval system within the European Economic Area. From 2006, marketing applications for biologics and for drugs used in the treatment of HIV, cancer, neurodegenerative disorder, diabetes and orphan drugs for rare diseases must be submitted to the EMA through a centralised procedure for marketing approval. As of May 2008, this was extended to included new substances treating autoimmune diseases and viral diseases. Marketing applications for other drugs that do not fall into these categories have the option of applying through

the centralised procedure to the EMA, or though mutual recognition or decentralised procedures for approvals in multiple countries. Separate national authorization procedures are available for approvals in individual countries. Approvals for generics and line extensions (additional indications) may apply through the centralised procedure to the EMA, or to the national regulatory bodies. Marketing applications for biosimilars have to be submitted via the centralised procedure to the EMA.

Committee for Medicinal Products for Human Use (CHMP)

The EMA comprises four bodies, of which the Committee for Medicinal Products for Human Use (CHMP, formerly known as the Committee for Proprietary Medicinal Products or CPMP), is responsible for formulating the EMA's scientific opinion on marketing applications for human medicines. This regulatory committee comprises scientific experts in medicinal product evaluation who are invariably employees of national regulatory authorities and are given responsibility for presenting an opinion to the board of the EMA on whether a new drug may be marketed. The board then reports to the European Commission, which issues the marketing authorisation.

Centralised procedure

Under the centralised procedure, a new drug sponsor submits its application directly to the EMA. At least seven months prior to submission of a marketing authorisation application, the drug company will notify the EMA of its intention to submit an application, and provide a summary of the drug. Following a review, the EMA, with input from the CHMP, determines if the product is eligible to apply under the centralised procedure. If the drug is deemed admissible, the submitted application is presented at the next monthly meeting of the CHMP, where one or two committee members (called Rapporteurs) are appointed to co-ordinate the evaluation of the application and prepare an assessment report. The national regulatory authorities of the appointed committee members then normally undertake evaluation, with assistance from experts from the European experts database. Once the evaluation has been completed and the report submitted to the CHMP, the CHMP issues a scientific opinion on the product. This opinion is then conveyed to the European Commission, which is authorised to convert the opinion into marketing authorisation, valid throughout the entire European Union.

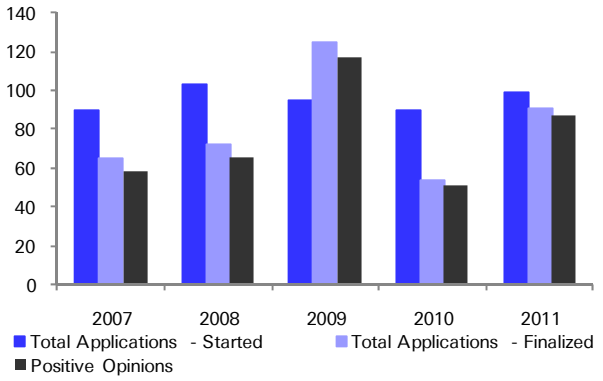
Around 120 days after the start of the process, the CHMP will usually adopt a list of questions and conclusions which are sent to the applicant. The clock then stops until the questions are resolved. For its part, the CHMP is obliged to issue an opinion within 210 days of receipt of an acceptable dossier. After the CHMP has issued its opinion, the EC has an additional 90 days to convert the opinion into a final decision. Hence, EMA guidelines state that the entire process should take no longer than 300 days. Once the drug is authorised, the EMA publishes a simplified, non-technical summary of the CHMP opinion for the public in the form of a European Public Assessment Report (EPAR), which is made available on their website.

Similar to priority reviews by the FDA, if a drug is deemed to be an innovative product of major public health interest (i.e. meets an unmet need), a request may be submitted for an accelerated assessment procedure prior to submission of the application. If accepted, the timetable for the CHMP will be shortened from 210 days to 150 days.

An issued marketing authorisation is valid for an initial duration of five years, after which it will need to be renewed on the basis of a re-evaluation by the EMA of the risk-benefits of the product. The CHMP will issue an opinion on the renewal application by 90-120 days, and if approved a second time, the marketing authorization is issued for an unlimited period unless the commission requests a second re-evaluation after another five years.

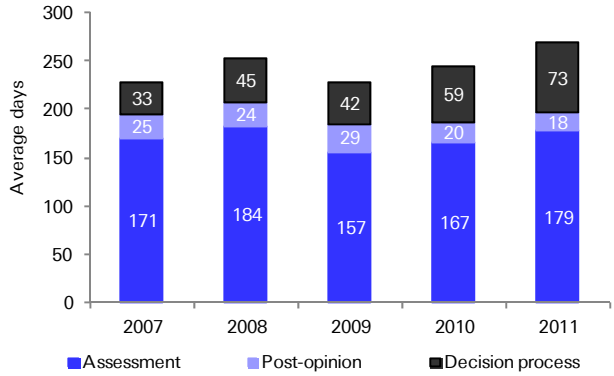
We can see from Figure 54 the effect of drug failures in the number of applications started which eventually get finalized, as companies withdraw their applications if there is a high probability of the drug not receiving approval due to disappointing clinical data. We can also observe that for the products which eventually get their applications finalized and submitted, a high proportion do receive a positive CHMP opinion, leading to approval. As seen in Figure 55, the agency works broadly within its self-imposed deadlines of 180 days for initial assessment, 210 days for adoption of CHMP opinion and 277 days for final commission decision. The review time may vary depending on complexity of applications for new substances.

Figure 54: EMA review statistics



Source: EMA

Figure 55: EMA review time – positive opinions



Source: EMA

Mutual recognition procedure (MRP) or decentralised procedure

Under the MRP system, an NDA is initially forwarded to one member state. If national authorisation is granted in that state, it allows for extension to one or more other member states. Under the MRP, the holder of the national authorisation for which mutual recognition is sought may then submit an application to other member states, certifying that the dossier is identical to the one for which first approval was granted (or explaining any differences). Within 90 days of receiving the application and assessment report, each member state must then decide whether to recognise approval. When such mutual recognition between member states is not possible, the EMA will arbitrate and the European Commission issues a binding decision.

The EMA also has mutual recognition agreements with other countries – Australia, New Zealand, Canada, Japan and Switzerland. These are based on assuming validity of good manufacturing practice (GMP) inspections conducted by other states. They allow for data sharing and lower additional requirements for EU approval of drugs already approved in these countries.

Regulation in Japan

Recent years have seen the Japanese regulatory system move towards that of the US. The previous system appeared to accentuate development and promotion of 'me-too' drugs and incorporated effective barriers to approval of drugs promoted by foreign firms. Indeed, until 1985, foreign firms were not allowed to apply without a Japanese partner during the first step of drug approval, and foreign test data were not accepted. Thus, a non-Japanese company that wished to introduce a product into the Japanese market was required to undertake duplicative clinical testing in Japan, with clinical trials conducted on native citizens. Clearly, this required significant additional investment, not to mention considerable delays in the time to launch.

Marketing license

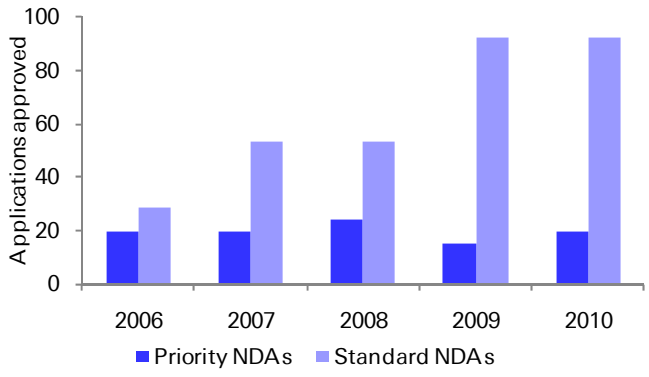
Until August 2002, the license granted in Japan (i.e. the approval) was one for manufacturing of the drug rather than its marketing. As such, companies seeking approval have had to manufacture their own product, a requirement that, by restricting companies' ability to out-source production, also led to significant inefficiencies among Japanese manufacturers. However, following a major revision in the Pharmaceutical Affairs Law (PAL) in 2002, this restriction was removed, and the granting of a manufacturing license is now distinct from that of a marketing license.

Approval times

Historically, approval times in Japan have been significantly longer than in Europe and the US. Recognising this weakness, the Ministry of Health, Labour and Welfare (MHLW) in 2004 merged the previous organizations involved in drug and medical devices approvals into a single agency, now called the Pharmaceuticals and Medical Devices Agency (PMDA). This agency is responsible for evaluating the quality, efficacy and safety of prescription drugs and medical devices.

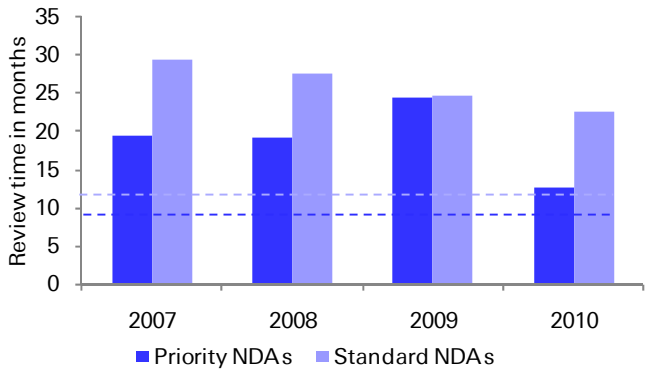
PMDA is required to meet targets specified by the MHLW in five year plans (second plan period: April 2009 to March 2014). The current plan stipulates that PMDA achieve a median (50%) regulatory review time of 9 months for new priority review products and of 9 months for new standard review products in the 2011-2013 years. A reference to the FY10 annual report shows that though review periods have shortened since 2007 – the median length of review time was 9.2 months for priority products and 14.7 months for standard products in 2010 – further improvement in efficiency is required to extend these targets beyond the 50th percentile (Figure 57). A mid-term plan launched in 2007 set targets by 2011 to reduce median regulatory time for generic drugs to 10 months, and for OTC drugs to 8 months.

Figure 56: Number of approved new drug applications



Source: PMDA

Figure 57: 80th percentile of median total review time



Source: PMDA

Evaluation process

Upon submission of the NDA to the PMDA, it is assessed by a panel of experts from various disciplines, which produces a Review Report. The NDA and the Review Report is passed on to the Evaluation and Licensing Division (part of the Pharmaceutical and Food Safety Bureau, MHLW), who consults with the Pharmaceutical Affairs and Food Sanitation Council (PAFSC), the Pharmaceutical Affairs Committee, and any other relevant committees as required. A new report is prepared in collaboration with the PAFSC, and if at this time, the manufacturer of the drug is also deemed to have passed a separate Good Manufacturing Practice (GMP) compliance review, the NDA and reports are passed on to the Minister, who issues the approval letter.

Funding and pricing of pharmaceuticals

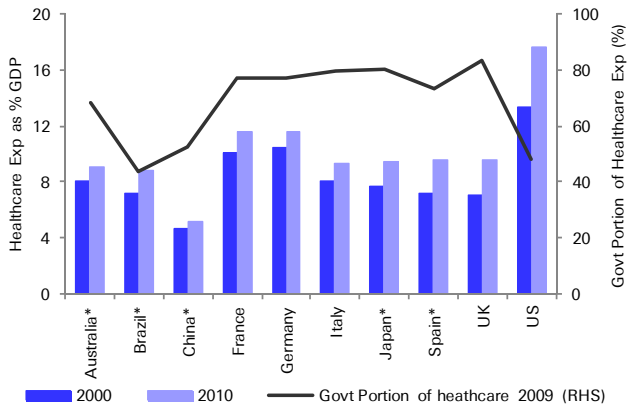
The burden of healthcare

The provision of healthcare is a major responsibility for governments around the world, with health services consuming a significant percentage of each government's budget. In addition, as people live longer and as the cost of providing medical treatment such as hospitalisation, medicines, surgery and nursing continues to rise, the provision of an acceptable level of healthcare for the population will become an increasingly heavy burden on those that pay for healthcare (Figure 58 and Figure 59).

While transferring healthcare provision to the private sector may reduce the funding burden, this is politically unacceptable in many countries, where citizens view the provision of healthcare as the responsibility of the state. As such, within the major industrialised nations, the US is the only country whose government continues to play a relatively minor role in the purchase and provision of healthcare for its citizens. The US is also one of only a few countries where drugs are freely priced. In many countries outside the US, it is the government which typically determines price and provision, with every effort being made to keep costs low. Prescription drug therapy is highly cost effective and often circumvents the need for other more expensive interventions such as surgery, hospitalisation, physician visits and nursing care later on. Nonetheless, prescription drugs also represent a significant proportion of healthcare costs. Expensive pharmaceuticals sold by highly profitable and private organisations represent an easy political target for governments seeking to slash costs to balance their healthcare budgets.

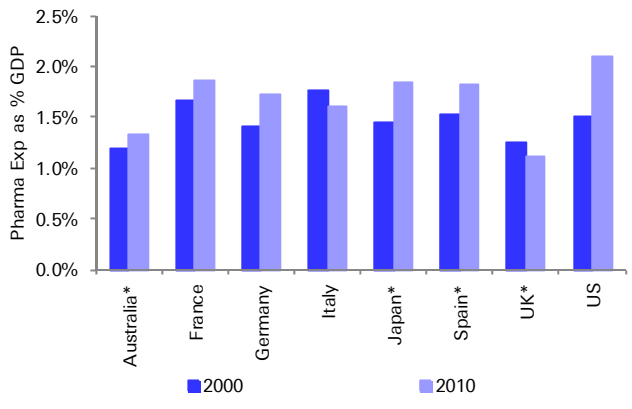
The variety of national models for the provision of healthcare means that almost every system has its differences. Starting with the US, the world's most significant economy and the pharmaceutical industry's most important market, we will provide a brief summary of the different models of healthcare provision in the major economies of the developed world.

Figure 58: Healthcare as a % of GDP (2000 and 2010*)



*Source: WHO, OECD, *2009 values*

Figure 59: Pharma costs as % of GDP (2000 and 2010*)

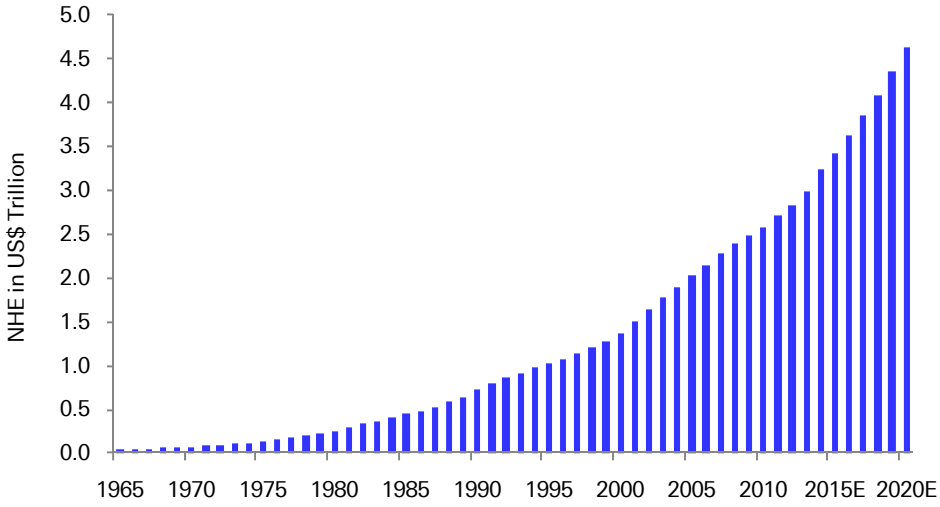


Source: WHO, OECD Health data, Deutsche Bank estimates
**2009values*

United States

The US currently spends a higher percentage of its GDP on healthcare than any other industrialised nation, a gap which has steadily widened over the past 20 years. In 2011, total national health expenditure in the US amounted to an estimated $2.7tr, or 17.7% of GDP. Importantly, healthcare expenditure as a proportion of GDP has increased by c.5% since 2000, when it was 13.8%. With the elderly population (>65 years) likely to rise to c.18% of the US population by 2025 from 13% today, we expect healthcare expenditures to rise further, placing more pressure on government budgets in the future.

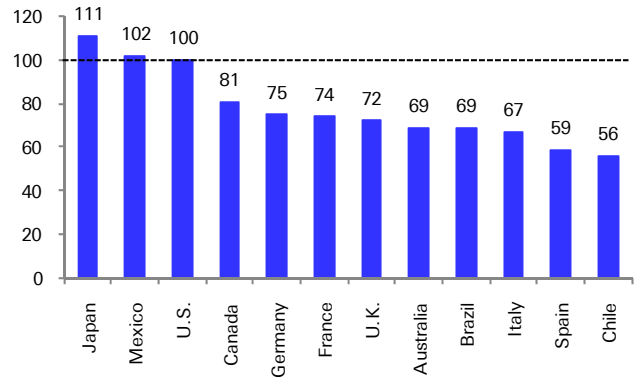
Figure 60: National health expenditure, US – 1965 – 2020E



Source: US Centers for Medicare and Medicaid Services

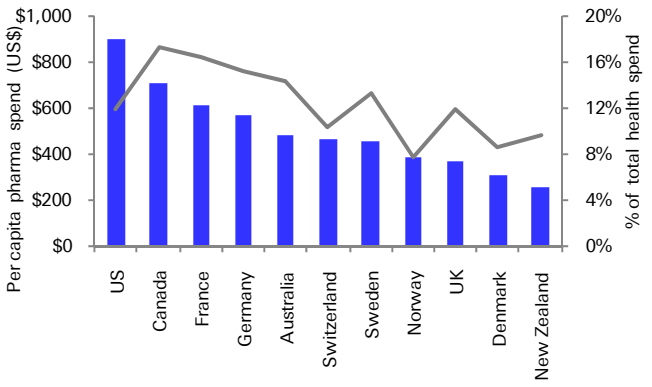
Rising healthcare costs have led to increasing calls for greater regulation of pharmaceutical pricing, albeit this is not the primary cause of rising healthcare costs. The US remains one of the few markets in which drug manufacturers are allowed to set the price of drugs without any government-imposed limitation. In addition, the import of drugs has been illegal, preventing wholesalers and users from taking advantage of substantially cheaper drug prices outside the US. As illustrated in Figure 61, the prices of branded drugs in the US continue to rank amongst the highest in the world. Per capita drug expenditure in dollar terms is also the highest amongst OECD countries (Figure 62). As European and Japanese authorities continue to target the cost of medicines as a means of controlling healthcare expenditures, the difference in prices between various countries appears likely to increase in the near term.

Figure 61: Index of global branded drugs prices (US=100)



Source: Danzon and Furukawa, Health Affairs, October 2008 (data collected 2005)

Figure 62: Pharma spend in OECD countries, 2010



Source: Commonwealth fund

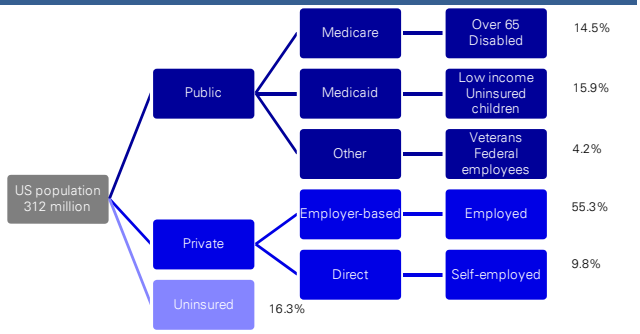
Managed care

The US government (through federal and state programs such as Medicare and Medicaid) and insurance schemes are the largest payors in healthcare. With the steady rise in healthcare costs in the latter part of the 20th century, the government and insurers began to explore ways of better managing healthcare expenditure. Managed care was developed as a system for controlling healthcare delivery to contain rising costs, while aiming to provide a certain standard of care. Managed care organizations sprung up, and were given the task of administering healthcare programs on behalf of the government and employers.

Managed care organizations (MCO)

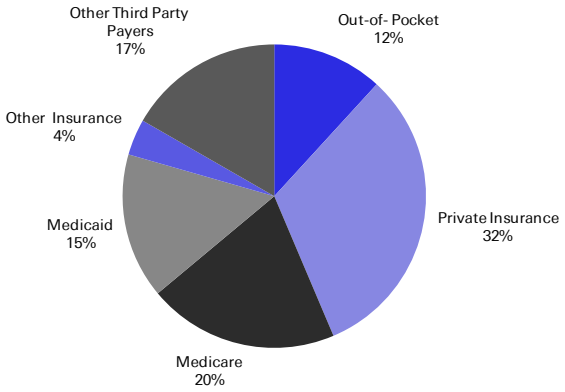
Using economies of scale and increased bargaining power, managed-care organizations leverage their large enrolment base to negotiate price concessions from drug manufacturers and health-services providers. Through their decisions on reimbursements of drugs and procedures, they play a large part in influencing patients' choices and the way care is delivered. As their fortunes are very much linked with their enrolees' health (a sick enrolee utilises more services), managed care organizations have also adopted a more holistic view of health, expanding their focus to patient education and preventive care, and have also implemented programs such as disease management, and case management programs to better control diseases and reduce hospital admission rates.

Figure 63: US coverage by type



Source: Income, Poverty, and Health Insurance Coverage in the United States: 2010, Deutsche Bank

Figure 64: Breakdown of 2010 US national health expenditure



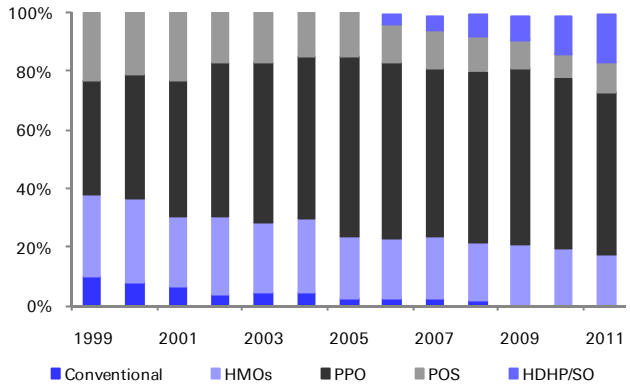
Source: Centers for Medicare & Medicaid Services

Around 90% of employed Americans now receive their healthcare benefits through a managed-care organisation. Over the past several years, a multitude of different organizations providing plans of varying flexibilities and benefits have been established. These include health maintenance organisations (HMO), preferred-provider organisations (PPO) and point-of-service plans (POS). The essential features of each are highlighted below.

- **Healthcare maintenance organisations (HMO):** HMOs are a type of MCO where patients are restricted to a group of physicians and hospitals which have a pre-existing contract with the HMO. In this model, patients select a primary-care physician who coordinates their care and acts as a gatekeeper in determining referrals to more expensive specialist care. A few examples of the different HMOs, in order of increasing flexibility, are:
  - **Staff model HMOs**: In this model, individuals see a doctor employed by the HMO who may prescribe drugs from an approved list (i.e. a formulary) set by their HMO.
  - **Group model HMOs**: Here, the doctor is self-employed and is contracted to work for one HMO. Again, less choice is available to the patient as their doctor must prescribe from a drug formulary determined by the HMO. Prescribing patterns are closely monitored and should the physician fail to adhere to formulary requirements, there is a risk of losing the HMO contract.
  - **Network HMOs and independent physician associations (IPAs)**: Within this type of organisation, doctors are under contract to a number of different HMOs, each of which typically runs its own formulary. It is invariably difficult for the physician to remember which drug may be prescribed under the different plans. The doctor is hence likely to prescribe what he feels is appropriate for the patient.
- **Point of service (PoS)**: Under point-of-service plans, individuals may select from a group of doctors specified by their insurer/plan manager. Patients wishing to see a physician outside the network or take up the services of a specialist will only be reimbursed if they have been referred by their primary-care provider. This differs from a HMO plan, where patients may only see physicians within the HMO network.

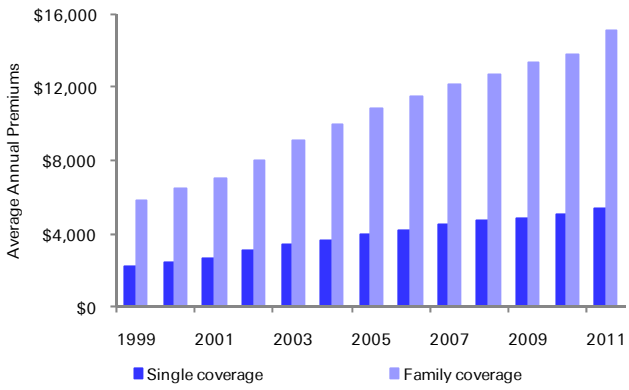
- **Preferred provider organisations (PPO)**: Under a PPO plan, patients need not designate a primary-care doctor and may choose to consult any doctor recommended by their plan manager. The patients pay a small co-pay each visit, while the remainder is reimbursed by the managed-care organisations. Physician charges are reduced in return for the volume of patients referred to them by the PPO. Patients may also consult a doctor who is not on the list, or even a specialist without a referral, but will be subject to a higher out-of-pocket co-payment. In general, premiums for a PPO would be higher than for a HMO and a PoS, a trade-off for choice and flexibility.
- **Fee-for-service (conventional)**: This is by far the most flexible of all health insurance plans and was the most common structure prior to the take-off of managed care. Under the 'fee-for-service' programme, individuals simply choose which doctor they wish to see and receive the treatment considered most relevant for their condition by the doctor. Rising premiums associated with the flexibility offered have seen patients switching to the aforementioned PPO and PoS programmes, which, while less flexible, are far more affordable.

Figure 65: Health plan enrolment by type



Source: Kaiser/HRET Survey of Employer-Sponsored Health Benefits 2011

Figure 66: Average annual premiums paid



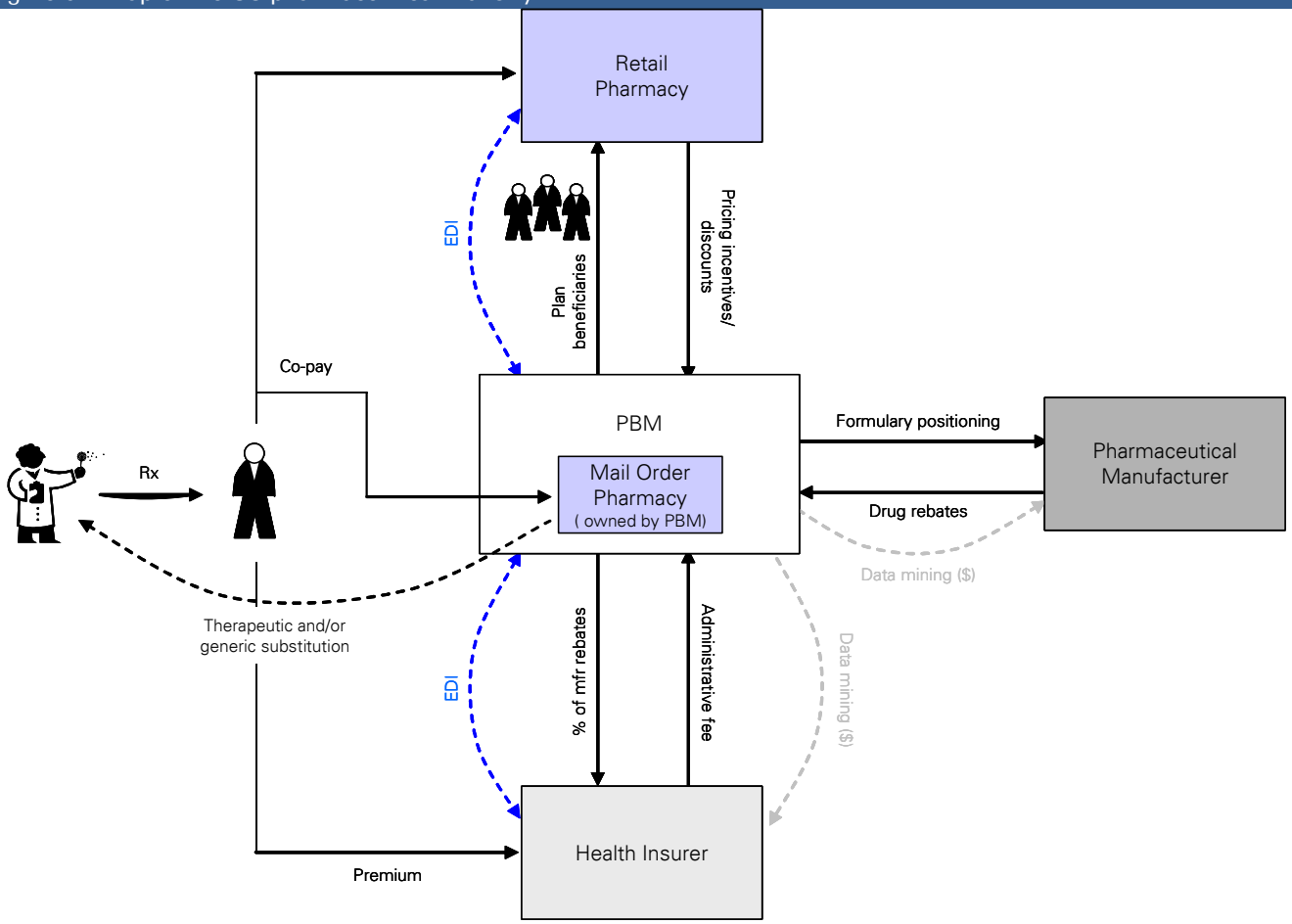
Source: Kaiser/HRET Survey of Employer-Sponsored Health Benefits 2011

Pharmacy Benefit Managers (PBMs)

Although managed care now looks after the healthcare needs of around half of the US population, the industry itself remains fragmented, with over 1,600 managed-care organisations operating in the US market today. Through outsourcing the dispensing of medication to other organisations called pharmacy benefit managers (PBMs), managed-care companies are able to reduce their medication costs even further through the greater mass and buyer leverage of the PBMs. PBMs are organisations which administer prescription drug benefits on behalf of insurers, HMOs and other drug sponsors. By aggregating purchasing and administration for plan members, they are able to save significant costs, not least through negotiating discounts on drugs with the pharmaceutical manufacturers themselves.

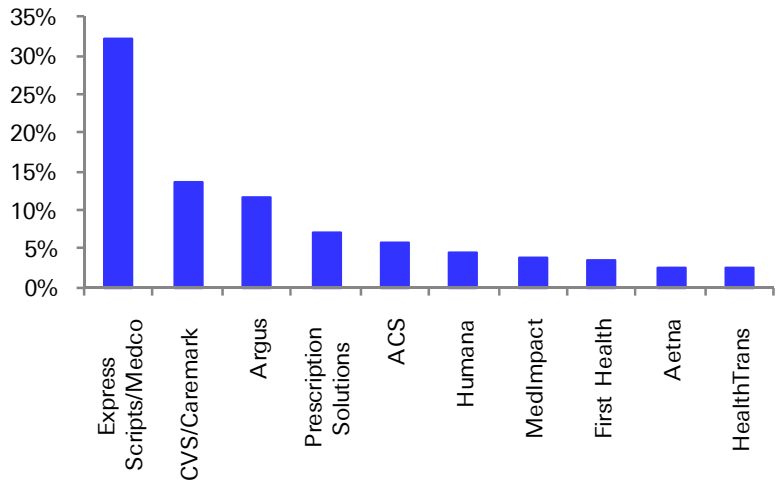
Over the past decade, the PBM industry has seen considerable consolidation, most recently the $29 billion acquisition of Medco by Express Scripts, which closed in 1H12. The combined entity now holds over 30% market share, while the top five companies command c.70% market share (Figure 68). Given that they design a significant proportion of HMO drug benefit plans, this provides them with substantial negotiating influence. More often than not, if large pharmaceutical companies want to have a new drug listed on a HMO formulary, they will need to reach an agreement on price with the PBM that manages the formulary. This high volume bargaining power places downward pressure on drug prices.

Figure 67: Map of the US pharmaceutical industry



Source: Deutsche Bank EDI = electronic data interface

Figure 68: PBM market share by Annual Rx volume, 2Q11



Source: Atlantic Information Services (AIS), Deutsche Bank

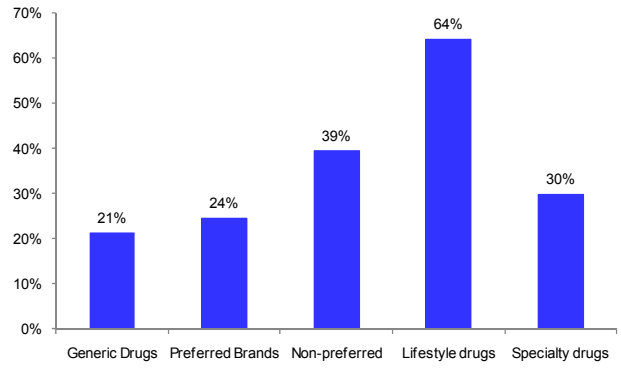
Co-payments and cost-reduction initiatives

For several years, managed-care companies have been trying to contain drug costs by initiating tiered co-payment schemes. These are basically payment plans whereby the consumer of the drug pays a differential co-payment for medicines, depending on the drug's status within the managed-care organisation's formulary.

The concept of co-payments is a simple one: The patient has a choice in the medication he or she wishes to receive, but depending on the tier, the patient will be required to pay a greater or lesser contribution towards the cost of the drug. In most multi-tier prescription drug programmes, generic drugs usually comprise the lowest tier, with the lowest co-payment required. The second tier is usually for preferred brands, where the co-payment is slightly higher. This group usually comprises branded drugs which are preferred because of safety, efficacy or because of a favourable negotiated price. The third tier is usually reserved for branded drugs and features a higher co-payment to share the cost burden with the patient and encourage the usage of tier 1 or 2 drugs. Finally, a fourth tier may exist which typically refers to drugs which require prescription by a specialist and are usually very expensive, and hence, have the highest co-payments. Drugs belonging to this category might include oncology drugs and biologics, e.g. TNF inhibitors. Beyond keeping costs down, the key feature is to inject price awareness into the consumer's decision and, subsequently, price elasticity into the pharmaceutical market. Having a tiered system therefore allows insurers to influence the consumer's choice, aligning their financial incentives with that of the insurer (Figure 69).

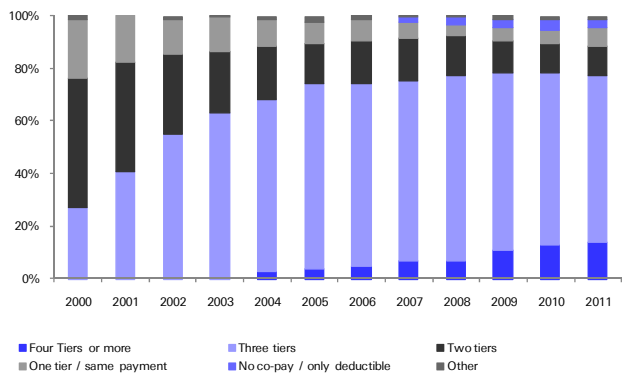
Initially, managed-care organisations began with two-tier programmes, comprised of two levels of co-payments depending on the patient's choice of branded or generic drugs. Three-tier programmes quickly followed, and gradually, an even greater number of tiers began to be built into plans. In an employee benefits survey of over 2,000 businesses conducted by Kaiser Family Foundation and the Health Research & Educational Trust in 2011, the majority of co-payment schemes have three tiers, with an increasing number of plans with four tiers or more being developed (Figure 70).

Figure 69: Average co-payment by tiers, 2011



Source: PBMI Prescription Drug Benefit Cost and Plan Design Report

Figure 70: Historical share of different tiered programs



Source: Kaiser Family Foundation & HRET Employer Health Benefits 2011 Annual Survey

Publicly funded health-insurance programmes

A number of federally funded programmes exist nationwide. Most significant among these are Medicaid for those with low incomes, and Medicare for the elderly and disabled.

Medicaid

Medicaid pays for hospitalisation, visits to doctors and prescription drugs for people with low incomes. It is funded jointly by the federal and state governments, and covers an estimated 56 million Americans, or about 18% of the total US population. In 2010, expenses for prescription drugs totalled $20.2 billion, out of total Medicaid expenditure of $401 billion. For the pharmaceutical companies, however, there is a cost associated with Medicaid business. Since 1990, passage of the Omnibus Budget Reconciliation Act (OBRA 90) required that in order to have a drug reimbursed by the Medicaid programme, the drug manufacturer will have to pay a rebate on the product supplied. These rebates were recently increased in 2010 as part of President Obama's healthcare reform (Patient Protection and Affordable Care Act). For all innovator products, reimbursement now requires a rebate that is the greater of 23.1% (vs. 15.1% previously) of the average manufacturer price (AMP) or the difference between the list price and the manufacturer's 'best price' (typically the discount offered to private managed care organizations). In addition, a further rebate is demanded for any price increase that exceeds the rate of consumer price inflation. Reimbursement for generic drugs requires a rebate of 13% (vs. 11% previously) of each manufacturer's AMP.

In addition to requiring rebates, as state budgets have become tighter, many state Medicaid programmes now have restrictive drug formularies, as well as limits on the number of prescriptions for which any patient may be reimbursed. Following the success of the states of Florida and Michigan in implementing formularies which require prior authorisation for reimbursement of non-approved products, several other US states are also looking at the use of restricted lists to contain expenditure on expensive new medicines. The provision of Medicaid benefits has also been increasingly outsourced to managed-care organizations as a means of controlling costs. Over 50% of Medicaid recipients are now enrolled in some form of managed care, of which there are three basic types. For reference, these are:

- **Full-risk capitation**, in which states contract with the managed-care provider and pay a fixed fee per enrolee per month to outsource the entire range of services to be covered under the insurance coverage.
- **Partial capitation**, in which some services are outsourced at full risk, while others are reimbursed by the state.
- **Primary care case management**, under which beneficiaries are assigned to case managers or primary care physicians, who are paid a fee to provide and coordinate care, referring patients to specialists when appropriate.

Medicare

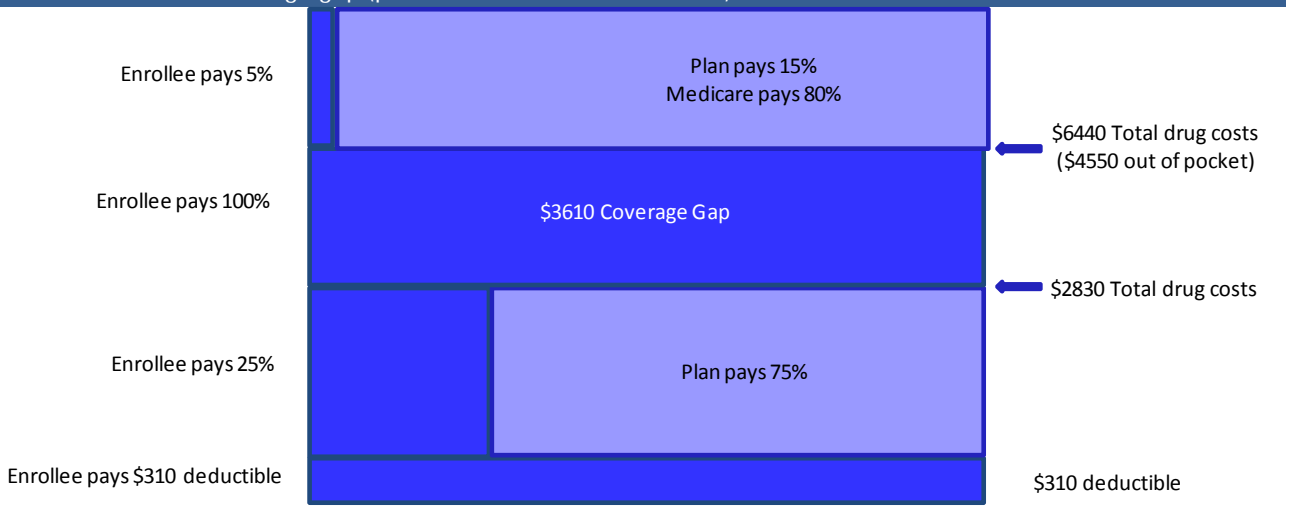
Medicare is a federal programme of healthcare for the elderly and disabled. In 2011, the programme cost the federal government $549 billion, $66.7 billion of which was spent on prescription drugs. Enrollment in 2012 is 50 million (41 million seniors and 9 million disabled), up from 47 million in 2010. Medicare coverage is divided into four parts:

- **Part A**: Also known as the Hospital Insurance (HI) program, this covers hospital services, along with limited skilled nursing and hospice care. Part A is paid for by a tax of 2.9% on earnings paid equally by employers and workers. As part of the healthcare reform of 2010, the tax component paid by high-income earners (more than $200,000 for individuals and $250,000 for couples) was increased from 1.45% to 2.35%. In 2012, an estimated 50.2 million people were enrolled in Medicare Part A.
- **Part B**: Also known as the Supplementary Medical Insurance (SMI) program, this covers physician care and certain outpatient, homecare and preventive

services. In 2012, c.46.6 million people were enrolled in Medicare Part B. Importantly, infusible drugs are covered by Part B, which offers pharmaceutical companies potentially better reimbursement terms than Part D (Average selling price (ASP) + 6% since 2005). From 2011, Part B has also been partially financed through a fee collected from pharmaceutical manufacturers.

- **Part C**: Also known as the Medicare Advantage program, this option enables Medicare beneficiaries to enroll in selected managed care or private fee-for-service plans. Such programmes provide at minimum the same coverage as the original Part B insurance in return for payments from Medicare. In addition, they may provide further benefits, such as prescription drug coverage, for the same or a slightly higher monthly premium. In 2012, an estimated 12.5 million people were enrolled in Medicare Advantage plans.
- **Part D**: At the inception of the Medicare Act in 1964, outpatient prescription drugs accounted for only a relatively minor component of healthcare and, as such, it was not considered necessary to include their reimbursement within the provisions of the Medicare Act. Since then, the cost of medication has risen significantly, particularly for the elderly, who suffer from multiple chronic conditions (e.g. hypertension, diabetes, arthritis, osteoporosis, etc). In November 2003, the US Congress passed the Medicare Modernisation Act (MMA 2003), which became active in January 2006. The plans are administered via stand-alone prescription drug plans (PDPs) or Medicare Advantage prescription drugs. In 2012, around 37.3 million people are enrolled on Medicare Part D.
- **'Doughnut hole'** - One of the issues with the Medicare Part D Act was the issue of the coverage gap, also referred to as the 'doughnut hole'. This represented the amount in excess of the Medicare Part D prescription drug coverage limit which had to be paid out-of-pocket, before the patient qualifies for catastrophic coverage. Figure 71 illustrates the doughnut hole prior to the healthcare reform in 2010.

Figure 71: Illustration of coverage gap (prior to 2010 healthcare reform)



Source: Kaiser Family Foundation illustration of standard Medicare drug benefit for 2010

Patient Protection and Affordable Care Act, and the Health Care and Education Reconciliation Act (2010)

These Acts were passed in 2010 as part of President Obama's effort to reform US healthcare, with the aim of ensuring universal access to health insurance. To fund the

cost of implementing the reforms, an annual levy is imposed on pharmaceutical companies which sell drugs to certain government programs (e.g. Medicare Part D, Medicare Part B Medicaid, Department of Veterans Affairs programs, Department of Defence programs and TRICARE). This levy will total $2.8 billion in 2012 and 2013, $3.0 billion in 2014-16, $4 billion in 2017, $4.1 billion in 2018 and $2.8 billion in 2019 onwards, and will be shared according to their market share of drugs sold to the programs, adjusted by a formula to ease the burden on companies with less sales.

To eliminate the doughnut hole, the pharmaceutical industry began to provide a 50% rebate on brand name drugs bought in the coverage gap from 2011. Medicare coverage aims to gradually close the gap by 2020, at which point enrollees will be responsible for 25% of the cost of both branded and generic drugs in the current coverage gap. This process began in 2011 for generic drugs and will begin in 2013 for branded drugs.

Figure 72: Pharma-related measures in the Patient Protection and Affordable Care Act

Measure	Detail
Medicaid rebates	Increases the Medicaid drug rebate percentage for brand name drugs to 23.1% [from 15.1%], effective January 1, 2010
Annual fees	Imposes new annual fees on the pharmaceutical manufacturing sector, according to the following schedule: $2.5bn in 2011; $2.8bn in 2012-13; $3.0bn in 2014-16; $4.0bn in 2017; $4.1bn in 2018; and $2.8bn in 2019 and later
Medicare 'donut' hole	For brand-name drugs, requires pharmaceutical manufacturers to provide a 50% discount on prescriptions filled in the Medicare part D coverage gap beginning in 2011, in addition to federal subsidies of 25% of the brand-name drug cost by 2020 (phased in beginning in 2013)
Biosimilars	Authorises the FDA to approve generic versions of biologic drugs and grant biologics manufacturers 12 years of exclusive use before generics can be developed
Comparative effectiveness research	Supports comparative effectiveness research by establishing a non-profit Patient-Centered Outcomes Research Institute to identify research priorities and conduct research that compares the clinical effectiveness of medical treatments

Source: Deutsche Bank

Though the US healthcare reform had a negative impact on the industry on its implementation in 2010 and 2011, we expect the incremental impact from 2012 onward to be minimal. In 2013, however, the sequestration process of the August 2011 Budget Control Act looks set to be triggered in an effort to reduce the federal budget deficit. This follows the recent failure of the "Super Committee" to reach an agreed debt reduction deal which was expected to have included the extension of Medicaid rebates to 'dual eligibles' (i.e. Medicare patients who have income below the threshold that would also qualify them for inclusion in Medicaid), which would have cut US pharma industry revenues by around $7 billion (2%) pa. While some congress members continue to seek a deficit reduction package in 2012, this looks unlikely to happen, particularly as political impetus will shift progressively towards the Nov-12 Presidential elections.

Thus, assuming the sequestration process comes into effect in 2013, this will result in, amongst other measures, a 2% (capped) cut to Medicare spending. All else equal, this will save $123 billion on Medicare expenditure between 2013 and 2021. Given that Part D drug spending accounts for 12% of Medicare expenditure, the pro rata negative impact on the US pharma market would amount to an average of $1.6 billion pa ($15 billion over 9 years) – equivalent to 0.5% off the market. This will place additional pressure on the pharma industry but we note that it will be incrementally much less negative than the first phases of Obama's Patient Protection and Affordable Care Act in 2010 and 2011.

Other federal programmes

Beyond Medicare and Medicaid, the federal government is also a major purchaser of pharmaceuticals for government-run institutions. Not least among these are the

Department of Veterans Affairs, the Defence Department and the Coast Guard. An estimated 20 million people are covered through such schemes.

Europe

The major difference between European and US healthcare is that the majority of European citizens obtain their healthcare benefits from state-organised programmes. In addition, governments in European nations exert significant control over the cost of care, either through price controls on prescription drugs, or reimbursement policies for prescription drugs sold within the country. The following is an overview of the systems in the major markets.

Germany

In Germany, health insurance is compulsory since 2009, though statutory health insurance funds (the Krankenkassen) cover the healthcare needs of around 89% of the population. Through these funds, citizens have equal access to healthcare benefits from providers who are under contract with the national system, or providers who are reimbursed directly by the funds.

For the employed, membership with insurance system is mandatory unless their income rises above an annually determined threshold. Contributions totaling c.15.5% (equally shared by employers and employees) of gross salary are deducted directly from the payroll. For the unemployed or the retired, the government funds this contribution. Civil servants, the self-employed and those with income exceeding the wealth threshold may choose to have private health insurance coverage instead and account for 11% of the population.

- **Reference pricing**: Previously, Germany did not apply any form of external price referencing with other countries, and was itself a reference country for many EU states. Hence, drug prices tend to be a premium in Germany. Germany had an internal reference price system, which covered about 75-80% of all drugs. However, this has changed with new laws enacted in 2011.

  The reference price system was first introduced in 1989 and has undergone several revisions since then. Under the current system, new drugs are compared with several reference groups (e.g. group 1 contains drugs with the same active ingredient, group 2 contains drugs in the same class, group 3 contains other drugs which are used to treat the same condition, particularly for combination products) in order to determine an appropriate reference price. For non-reference priced patented drugs, manufacturers are required to grant a mandatory 16% discount to pharmacies, unless they offset part of the discount by voluntary discounts or price reductions.

  Under the revised system (AMNOG), new drugs may be allowed to set their prices for the first 12 months post launch. A cost-benefit analysis is then launched within three months of introduction by the Institute for Quality and Efficacy in Health Care (IQWiG). For all new drugs, the manufacturer must prove the benefits over available comparable products, failing which the drug will be added to the reference pricing list. At the end of one year, drugs that demonstrate additional benefit can be priced as per negotiation between manufacturers and insurers. The German government estimated savings of more than €2.2 billion pa on implementation of these reforms.

A price freeze has been enforced for all drugs sold at retail pharmacies, from August 2010-December 2013. The objective is to prevent manufacturers from artificially raising prices just before an increase in mandatory discounts.

- **Co-payments**: Co-payments of pharmaceuticals are set at 10% of retail prices, with a minimum of €5 and a maximum of €10, up to a cap of 2% of gross income per year. In addition, if the price of the drug is higher than the set reference price, that difference will also be borne by the patient (a top-up co-payment). However, drugs priced more than 30% below the reference price are exempt from co-payment.
- **Generic pricing**: Generic drugs can be priced freely but are subject to a mandatory 10% discount unless they are priced at least 30% below the reference price level. An additional 6% discount is also applicable for non reference priced generics. Biosimilar drugs are included in the same level 1 reference pricing system as the original drug if they have the same amino acid sequence.
- **Generic substitution:** The law in Germany allows pharmacists to substitute branded drugs with its generic equivalent if the dosage strength, formulation and pack size are similar, unless the doctor has specifically indicated for the branded drug to be prescribed. Pharmacists are also required to substitute drugs under voluntary discount agreements, where applicable. This has contributed to an increase in market share of imported pharmaceuticals.
- **Prescribing controls**: Physicians are legally bound to prescribe economically. In addition, annual agreements between physician groups and health insurers set targets (prescribing controls) that include guidelines for the volume of generic prescriptions and the minimum average cost price per drug.

France

France has a social insurance system which provides near universal coverage. The main scheme (Régime General) provides coverage for around 87% of the population, and is predominantly financed through compulsory contributions made by employees and employers. Around 93% of the population has additional contracts with one of the supplementary sickness funds (including mutuelles, which are not-for-profit providers) which cover private medical insurance and out-of-pocket payments.

In an effort to contain overall healthcare costs, the government closely controls the supply of prescription drugs in its capacity as both regulator and the industry's largest customer. Several schemes have been implemented:

- **Pricing and therapeutic assessment**: Once approved, new drugs are priced after an evaluation by the Comité Economique des Produits de Santé (CEPS) and Commission de la Transparence (CT). The CT examines the product dossier and assesses the medical benefit (SMR) and the improvement in medical benefit (ASMR) based on comparisons with other drugs in the same therapeutic class. The medical benefit (SMR) is assessed based on criteria of efficacy and safety, therapeutic alternatives, disease severity, treatment type and public health impact. A medical benefit level is then assigned, which may be major, important, moderate, weak or insufficient for reimbursement. In the next step, the ASMR compares the new drug with current products or therapies. This may be within the same class or for treatment of the same disease. The drug is then assigned an ASMR level of 1) major therapeutic progress, 2) important improvement, 3) moderate improvement, 4) minor improvement, 5) no improvement.

In the second stage, prices of reimbursable pharmaceuticals are negotiated between the drug manufacturer and the CEPS, in light of drug sales forecasts for a five-year period. Drugs with ASMR ratings of 1-4 may be priced higher than existing therapies, while a drug with ASMR 5 will not be granted a price higher than existing therapies. In addition, though there may be no formal external price referencing, the CEPS have been reluctant to allow prices to be set higher than the average price in the EU (especially the lowest price of Germany, Spain, Italy and the UK). However, a price guarantee ensures that prices for drugs with ASMR 1-3 will not be lower than the lowest price in these markets.

Simultaneously, following the SMR and ASMR assessment, the reimbursement rate is then set by the National Union of Health Insurers (Union Nationale des Caisses d'Assurance Maladie, UNCAM). Reimbursement rates are usually set at 65% for SMR major or important, 30% for SMR moderate, 15% for SMR weak and 0% for insufficient. UNCAM has the flexibility to set reimbursement rates within a 5% range on either side of these figures if it wishes. Non-reimbursable drugs and most hospital-only pharmaceuticals may be freely priced.

- **Price cuts and rebates**: The price for each drug is re-evaluated every five years, to ensure it has a reimbursable SMR; drugs with insufficient SMR are periodically de-listed from the basket of reimbursable drugs. Drug manufacturers are also obliged to refund some of the difference if reimbursements exceed manufacturer forecasts at the time of applying to CEPS. In addition to the scheduled reviews, price cuts for a specific drug may also be implemented based on higher than expected sales, on commercialisation of cheaper drugs for the same indication and on national pharmaceutical spending growth targets. The French market is also subjected to targeted price cuts under the Social Security Finance Law; such cuts generated €320m and €548m saving in 2009 and 2010, respectively, while the 2011 estimate was around €500m. The 2012 Social Security Finance Bill included a 2.5% cap on annual healthcare expenditure growth, in addition to an increase in tax payable by drug manufacturers on gross reimbursed turnover (from 1% to 1.6%).
- **Generics**: To encourage use of generic drugs, generic substitution of branded drugs has been allowed since 1999, unless specifically indicated by the physician. Generics are usually priced at a minimum of 55% discount to the original branded drug. In addition, 18 months after a drug goes off-patent, the price for the branded drug as well as for its generics are cut, unless it is already included to price controls through the reference pricing system. Attempts to set generic reimbursement levels at the price cheapest product through changes in the Social security Finance Bill have not been successful so far. As part of a five-year agreement between UNCAM and physician unions, physicians are now eligible for performance-related fees based on generic prescription targets for specified drug classes.

United Kingdom

The UK's National Health Service (NHS) was established in 1948 to provide universal healthcare to all residents. Typically, individuals register with a general practitioner (GP) in their locality. This GP is then responsible for providing general healthcare services and referring patients to hospital specialists when necessary.

The NHS is financed partly by the government and partly from national insurance premiums, paid at source by employers and employees. Around 12% of the population

currently has some form of private medical insurance, although most plans do not pay for ambulatory drugs.

Dispensing of prescription medicines in the UK is either undertaken directly by the GP or, more commonly, through presentation of a GP-written prescription at a pharmacist. Prescriptions are free for certain segments of the population (e.g., the elderly, students, people on low incomes), with the NHS reimbursing the pharmacist or doctor for the full cost of the drug and paying a fee for dispensation. However, for the vast majority, a prescription charge of £7.65 is payable per prescription, irrespective of the actual cost of the drug prescribed. Patients may also purchase a Prescription Prepayment Certificate (PPC), which consists of a fixed upfront cost of £29.10 for three months or £104 for a year, and covers all NHS prescriptions within this time period. Prescription charges collected are then used to offset the amount owed by the NHS.

Drugs may fall into one of three categories – 1) prescription-only medicines, 2) pharmacy-only medicines (pharmaceuticals which may be dispensed by a pharmacist) and 3) pharmaceuticals on the General Sales List (GSL), otherwise referred to as OTC. Prescription-only medications which have been approved but placed on any of two negative lists ('black' and 'grey' lists) may not be eligible for reimbursement. The 'black' list includes drugs that are not allowed to be prescribed on the NHS and must be paid out-of-pocket by patients, while the 'grey' list refers to drugs that may be prescribed for certain indications or diseases.

At the present time, pharmaceutical expenditure in UK accounts for c.12% of the total healthcare budget and continues to increase. The government has sought to contain drug costs in a number of ways:

- **Pricing**: Reimbursements of drugs are subject to the Pharmaceutical Price Regulation Scheme (PPRS), which is a profit framework negotiated and agreed upon by the Department of Health and the Association of British Pharmaceutical Industry (ABPI). The PPRS sets out terms which allow drug manufacturers a defined return on capital and profit each year. If returns exceed the agreed-upon target, the excess will need to be paid back to the NHS, but if returns are too low, the company may apply for an increase in price. The manufacturer may also apply for an increase or decrease in its original price, in view of new clinical evidence of efficacy in the previous indication, or in a new indication. Each PPRS agreement lasts for five years, with each renewal usually involving negotiated price freezes or price cuts by drug manufacturers. The current PPRS was initiated in 2009, and is effective up to 2013, when a value based pricing system is likely to come into force (see below). Drug manufacturers that do not participate in the PPRS may have their drug prices determined by a range of factors, subject to the statutory Health Service Branded Medicines Regulations. In contrast to other EU countries (with the exception of Germany), there is no external price referencing with other EU countries throughout this process.
- **Usage**: A body called the National Institute for Health and Clinical Excellence (NICE) was established in April 1999 to review the cost effectiveness of medicines and discourage their use if their cost outweighed their perceived benefits. Although NICE was designed to be a positive system to ensure effective drugs were used and paid for, primary care trusts and their respective GPs now only prescribe medicines once they have gained NICE approval, effectively delaying and discouraging the use of new treatments. In addition, companies now negotiate with NICE on price and usage, often coming to a

mutually acceptable 'deal' before approval is gained – this effectively means that the UK is no longer a country with free pricing.

- **Generics**: Generic substitution is not permitted, though physicians are encouraged (and trained) to prescribe using the International non-proprietary name (INN), assisted by the use of prescribing software that lists drugs by INN. Physician-level prescribing incentives encourage this practice. Unbranded generics are not included under the PPRS and manufacturers are free to set prices, as long as they do not exceed the price of the branded drug. However, generics are included in Category M of the Drug Tariff for reimbursement, which are revised quarterly to ensure that pharmacy profits remain within agreed-upon targets.
- **Value-Based Pricing:** The PPRS will not be renewed on its expiry in 2013 – it is likely to be replaced by a value-based pricing system, effective January 2014. Under the new system, a range of price thresholds will be designed for new drugs based on their levels of value. Beyond the 'basic' threshold for drugs at par with existing therapy, new drugs would be classified under 'therapeutic innovation', 'burden of illness' or 'wider societal benefits', based on quality-adjusted life years (QALY). All drugs priced at or below the basic threshold will be granted reimbursement, while those claiming additional value would be required to provide evidence. The definitions of these value levels and the kind of supporting evidence required is yet to be finalized, as, indeed, are most of the finer points of the proposed system

Figure 73: Overview of pricing and reimbursements in select European countries

Country	Denmark	Greece	Italy	Netherlands	Spain	Sweden
Pricing	Reimbursement prices are determined by the cheapest drug in the same substitution group. For first-in-class drugs, price proposed by the company may be accepted if it is deemed reasonable for its therapeutic value.	Reference pricing is used to determine prescription drug price at the average of the three lowest prevailing prices in EU countries.	Therapeutic value and cost effectiveness are considered to determine pricing. Price comparisons with other European states are also taken into account and the Europan average is usually set as the maximum permissible price.	For novel drugs, calculated as the average price of the drug in Germany, France, Belgium and the UK (min. 2 countries). Therapeuticaaly interchangeable drugs are reimbursed according to a reference pricing system, which is the drug price at or below the average price of drugs in the group.	The reference pricing system (drug prices in EU15, including the lowest price), budgetary impact, comparable effectiveness vs similar drugs and manufacturer profit levels are considered.	Prices may be freely set and eligible for reimbursement provided they are deemed to be "reasonable", which is determined by a set of criteria set forth by the Pharmaceuticals Pricing Board (LFN). This includes human value and cost-effectiveness.
Reimbursement	Need-depending (proportional) co-payments, where patients pay a percentage of the reimbursement price, depending on the sum of their payments in last 12 months.	Reimbursement set at 75% , 90% & 100% for standard medicines, chronic conditions and for severe life-threatening conditions, insulin and drugs for pregnancy resp. A positive drug-reimbursement list released in Sept-2011; reimbursement to be limited to cheapest drug in each class.	Prices of reimbursable drugs (designated “class A pharmaceuticals” generally, and “class H pharmaceuticals” if they are only reimbursable in hospitals) are fully reimbursed.	Drugs are fully reimbursed up to their reimbursement prices, which pharmaceutical companies adhere to. Hence, there is seldom any out-of-pocket payment required.	Reimbursement is set at 100% for hospital drugs, 90% for drugs treating chronic diseases and 60% for all remaining drugs. Pensioners and some groups of patients (e.g. disabled) are not required to make co-payments. A negative reimbursement list exists.	The patient pays out of pocket for the first SEK900 costs. This is followed by a tiered co-payment scheme until SEK4300, after which any further costs are fully reimbursed (max. total out-of-pocket is SEK1,800). This is calculated over a 12 month period.
Generics	Generic versions of drugs are automatically granted reimbursement provided their price is lower than the branded drug. Denmark has mandatory generic substituion.	Maximum price for generics is set at 60% of the originator's price. This cap was lowered from the earlier 80% to improved generic penetration (current 16%).	Prices of generic drugs must generally be at least 20% cheaper than the original branded drug in order to be reimbursable. Generic substitution is mandatory.	In each reference price group, only the cheapest generic is reimbursed. In contrast with other countries, generic substituion requires the approval of the physician and the patient.	Generic drugs follow the same pricing procedure as reimbursable prescription drugs; the first generic for a drug must be priced 40% below the original brand. Generic substitution is now mandatory, with reimbursement level set for cheapest active ingredient.	Generics may be freely priced provided it is not the most expensive in the class. If the patient qualifies for reimbursement, this is calculated according to the cheapest drug in the group. Mandatory generic substitution is in place.
Recent Reforms	A price-cap on prescription drugs was extended for 15 months in December 2011. The cap can now be adjusted by 1.5% in April 2013.	Cost-containment measures limit the FY12 drug spend to EUR2.88b. A new law mandates that physicians prescribe drugs by generic names. Pharmacy margins are to be capped at 15%.	Among other cost-saving measures over 2012-14, 35% of excess hospital drug spend beyond the target to be covered by the manufacturer, new patient copayments, higher VAT rates.	-	Cost-effectiveness assessment to be part of pricing and reimbursement process, mandatory 15% discount on drugs older than 10 years with no generic versions.	Sweden initiated a process to review feasibility of a EU reference pricing system and may also introduce reimbursement limits on certain products.

Source: Deutsche Bank, IMS HEalth

Japan

Japan has a compulsory health insurance system in which everyone living in the country must participate. The insured pays insurance premiums to the government and is covered for up to 90% of the cost of medical services and prescription drugs. Some co-payment is invariably required, but the bulk of the cost is paid by one of two government-controlled health insurance programmes. Private supplemental health insurance is available to cover co-payments or non-covered costs.

Individuals either take part in the Employees' Health Insurance Plan or the National Public Health Insurance Plan if they are not eligible for the employees' plan.

- **Employee's Health Insurance (EHI) Plan**: This plan is designed for individuals who are in full-time employment. It also covers their dependants. The premiums are paid equally by employee and employer, and are deducted at source.
- **National Health Insurance (NHI) Plan**: This plan covers the self-employed, students, certain industries such as agriculture, forestry and fishery, and the unemployed. Premiums are similar to those under the EHI plan.

Patient co-payments are part of both plans, with co-pay level set at 30% for ages 6-69 years, 20% for ages 70-74 years and 10% for age over 75 years. While children below 6 years and people with certain disabilities are eligible for lower co-payments, the unemployed are exempt. In addition to co-payment limits, deductible levels are also set for each age category. If patient expenses exceed the deductible, the excess is reimbursed by the government.

In Japan, there is no requirement for a referral in order to see a specialist, and patients are allowed to see any doctor they wish without the need for an appointment. In addition, most hospitals and clinics in Japan are private institutions, with no central control over healthcare resources. As a result, McKinsey estimates that compared with other developed countries, Japan has three to four times more CT, MRI and PET scanners, twice as many hospitals and three times as many hospital beds on a per capita basis.

Hospitals and physicians are reimbursed through a fee-for-service model, with no system of audit of costs, which encourages the ordering of investigations and procedures, prescriptions and increasing lengths of stays in hospitals. Reimbursements for services are standardized through a Medical Fee Table, while prices of pharmaceutical drugs are set according to a NHI Drug Price List. Both these lists are set by the Ministry of Health, Labour and Welfare (MHLW). The government has traditionally relied on the regular cutting of prices and fees to control healthcare spending, which may be an unsustainable trend given the expected rise in healthcare costs due to Japan's ageing demographics.

- **Pricing**: The MHLW's Health Policy Bureau evaluates all new drugs based on their therapeutic value and costs, and sets prices based on comparison versus existing drugs in the same class, or based on an estimated profit allowance, where such comparators are not available. Japan's NHI Drug Price List contains the list of drugs for which healthcare providers receive reimbursement under the health insurance program. Normally, a difference exists between the purchase price paid (through discounts offered by drug manufacturers) and the NHI reimbursement price, the difference of which goes towards the income of the hospital/physician. The MHLW reviews the drug price list every two years

in an effort to reduce this difference. At this time, a survey of wholesalers, hospitals and clinics of the prices of all drugs covered by insurance plans is undertaken. The price is then calculated as a weighted average of the sales price and current reimbursement prices with adjustments for the consumption tax. Hence, it is important to note that drug prices for reimbursements are usually revised downwards every two years in Japan in a regular price revision process (Figure 74).

- **Reimbursement**: Drugs on the NHI list are fully reimbursed at the listed price, after deduction of patient co-payments, which vary depending on the patients' age and income.

Figure 74: Revision rates on reimbursement prices in Japan

Year	1992	1994	1996	1997	1998	2000	2002	2004	2006	2008	2010	2012
Revision Rates	-8.1%	-6.6%	-6.8%	-3.0%	-9.7%	-7.0%	-6.3%	-4.2%	-6.7%	-5.2%	-5.8%	-6.3%

Source: Pharmaceutical Administration and Regulations in Japan by JPMA

- **Generics**: Generic drugs are now added to the NHI Drug Price List twice a year (in May and November from 2009). The price of the first generic drug is set at a minimum discount of 30% to the branded drug price, and prices of subsequent generics are set equivalent to the lowest priced generic version on the list. When there are more than 20 generic versions on the list, the price is cut to 90% of the lowest existing generic price.

Generic drugs

Introduction

Once the patent or period of exclusivity expires on a branded product, sales are likely to be subject to competition from generic versions of the active molecule, most particularly when sales of the branded product are significant (in excess of $100 million per annum). A generic drug is one that its manufacturer has demonstrated to be 'bioequivalent' to the patented product, i.e. it has the same pharmacokinetics and availability in the body. Because the attributes of a generic drug are the same as the branded or innovator drug (in effect, they are the same molecule), its only differentiation from the branded drug is its price.

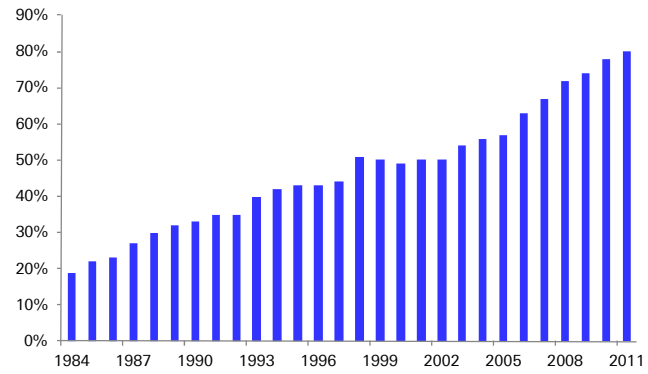
Hatch-Waxman Act established today's generic industry

The modern generics industry in the US was established following the 1984 Hatch-Waxman Act. In return for allowing innovator products greater market exclusivity, the Act allowed the generic manufacturer to use the product innovator's drug safety, efficacy and toxicology data when filing for FDA approval. This greatly reduced the cost of generic applications and the time taken to gain approval. In essence, the generic manufacturer merely needs to demonstrate that its version of the drug was bioequivalent (identical) to the branded drug.

Generics market

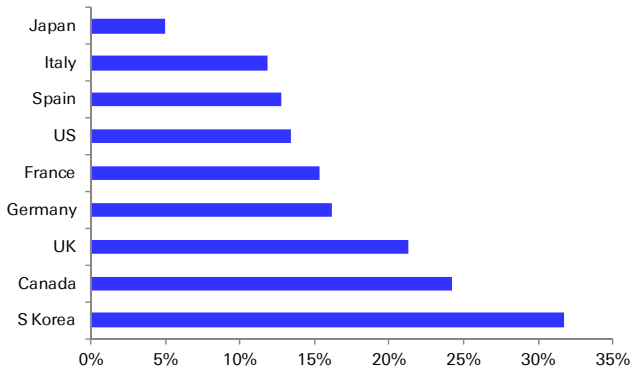
This Act has contributed to the strong growth of the US generic market. As demonstrated in Figure 75, in 2011, generics accounted for c.80% of the prescription drugs market by volume, compared to 19% in the year the law was first enacted (1984). With several blockbuster drugs (annual sales >$1 billion) facing patent expiry over the next few years, and countries looking to cut spending in order to balance their fiscal budgets, we expect generic drugs to continue to gain further market share (Figure 76).

Figure 75: Generic drug share of US prescription market



Source: IMS Health

Figure 76: 2010 Generic share of pharmaceutical spend

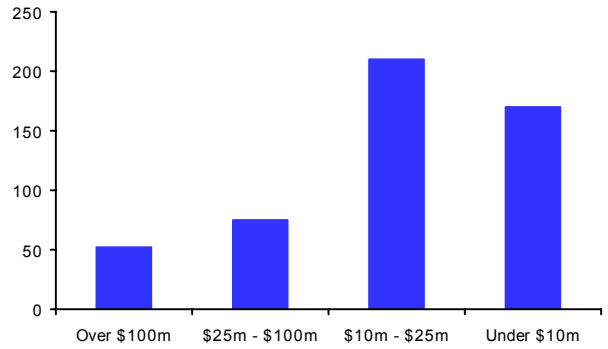


Source: IMS Health

In general, once the patent/exclusivity period for a branded product expires, generic competition will commence almost immediately. As more and more generics enter the market, price erosion will intensify. As we can see from Figure 77 and Figure 78,

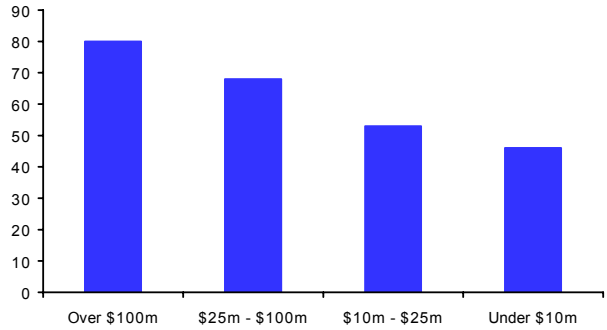
branded drugs with sales of more than $25m, especially if they are greater than $100m, attract generic entrants rapidly from the moment their patent expiries. Depending upon the number of entrants, it is not unusual to see generic prices in the US market at only 20% of that of the patented product. Today, as illustrated in Figure 80 by the generic erosion chart for AstraZeneca's Seroquel, the influence of managed care and modern technology on buying patterns has shown that most large products facing patent expiry can expect to lose between 80% and 90% of their monthly US revenue within two months of expiry. This contrasts with Figure 79 which shows a typical 70-80% decline over 12 months seen with Zantac in the late 1990s and bears testament to the present efficiency of the US system.

Figure 77: Days to first generic entrant



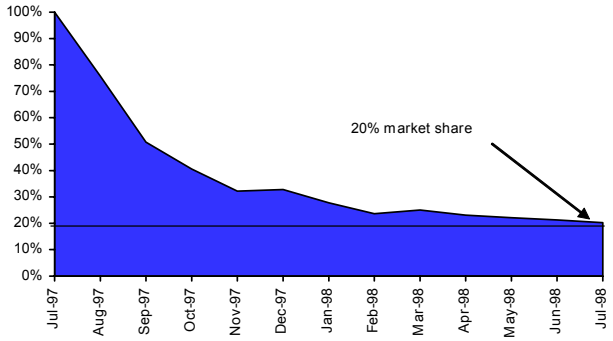
Source: Health Services Research

Figure 78: Percentage with generic competition



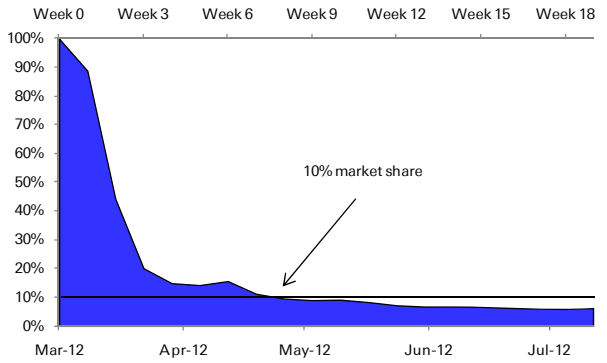
Source: Health Services Research

Figure 79: Zantac patent expiry (% sales lost, 1997)



Source: IMS Health

Figure 80: Seroquel patent expiry (% sales lost, 2012)



Source: IMS Health

Generic erosion

The extent of generic erosion varies in different geographic markets depending on both legislation and physicians' attitudes towards costs. Erosion of branded drugs tends to be most rapid in the US, driven by the profit opportunity and the desire of private managed care organizations to keep costs down (note that the prices of branded drugs are around 30-40% higher in the US compared to other countries; US generics are typically priced at a 80-85% discount to branded drugs).

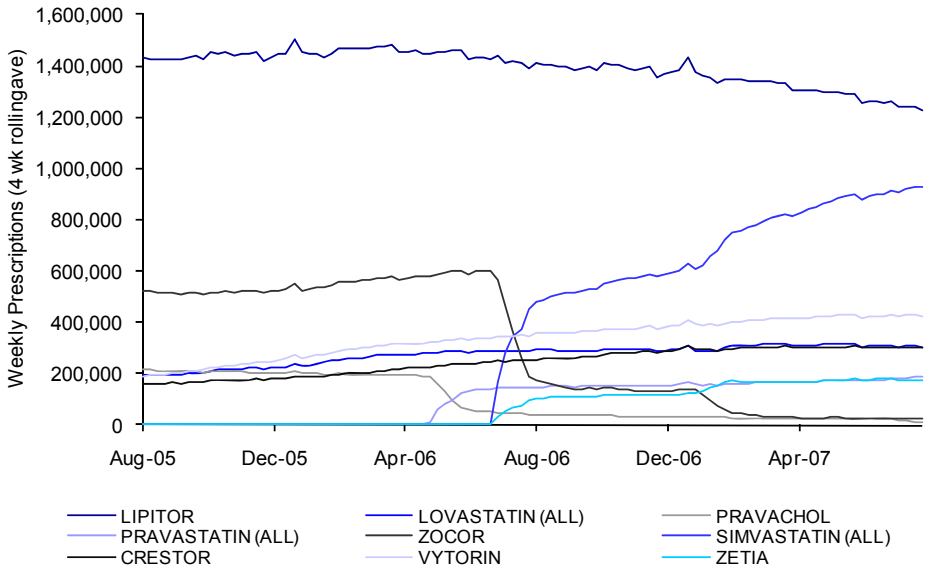
It is worth noting that the price differential between branded and generic prices is much greater in the US as compared to many other countries and thus the cost savings to be

achieved by the insurer or government are much greater. In contrast, in many European countries, for example, generics are often priced at only a modest discount to the branded price. However, the pressure on government budgets across Europe means that we expect increased pressure and incentives to promote generic markets as a means of containing the growth in prescription drug expenditure. As such we expect generic erosion rates to accelerate versus previous norms.

Therapeutic substitution

We now know that the loss of patent protection results in significant generic substitution of a branded drug. This may also potentially result in a meaningful deterioration in the growth of other drugs in the same class, as physicians substitute a patented, branded drug with a cheaper generic in the same therapeutic class, i.e. therapeutic substitution. As the benefits of one drug over another in the same therapeutic class become more marginal and cost becomes a more significant issue, the case for driving therapeutic substitution will become stronger. Indeed, looking at recent expiries, it does now seem that in classes where products are poorly differentiated, the advent of generic competition against the category leader results in a moderation in the growth profile of the entire class. This is illustrated by the impact of the patent expiry of Zocor on other branded statins (Figure 81). Following the patent expiry of Zocor, sales of the bestseller Lipitor also experienced a gradual decline, as physicians and patients switched to simvastatin (generic version of Zocor).

Figure 81: US statin market following Zocor patent expiry



Source: IMS Health

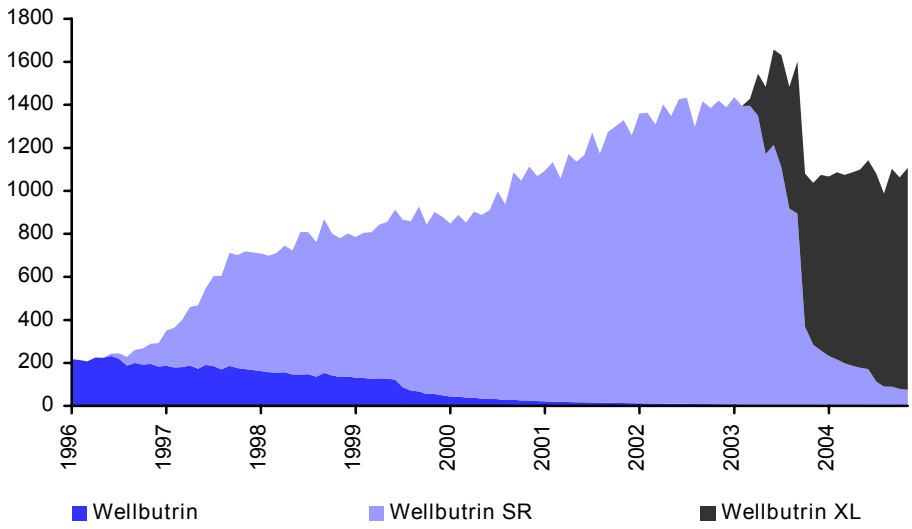
Patent life-extension strategies

The threat of a large impending patent expiry for any leading research-based company should not be underestimated. Indeed, for a drug with $1 billion of annual sales, each day that generic entry is deferred is worth at least $2.7 million to revenue and probably well over $2 million to gross profits. This is a definite incentive to defer the inevitable day of reckoning.

Not surprisingly, the leading pharmaceutical companies have developed several strategies to extend the life of their products, with varying degrees of success. These range from the now almost inevitable litigation to altered formulations and isomers of existing drugs:

- **Litigation**: Almost all pharmaceutical companies will have in place a host of patents surrounding any one drug. Beyond the strongest composition of matter patents, these invariably include patents surrounding the active molecule's formulation, its mechanism of action and its manufacture. At the slightest whiff of a generic threat, litigation inevitably follows, with some form of patent infringement being cited. If the first court ruling goes against the innovator, there is usually the opportunity to appeal. Litigation sometimes buys the innovator several months of extra time as the litigation process very often runs beyond the patent expiry date.
- **Formulations**: An innovative approach to life cycle extension is to develop an alternative formulation of an existing drug late in its life cycle which offers patients and physicians a definite benefit, yet poses a further challenge to the generic manufacturer. For example, moving from a three-times-a-day formulation to once a day offers compliance benefits for patients, which will be recognised by physicians and yet probably presents an additional challenge to the generic (i.e., developing its own formulation for slow release). Of course, if the generic company is able to develop its own formulation, then the life extension strategy could falter. However, strong formulation competence may fall outside the capability of some generic companies. Thus, the more sophisticated the formulation, the greater the protection. A good example is GlaxoSmithKline's Wellbutrin franchise: the original formulation of Wellbutrin, first introduced in 1985, required administration three times daily. The company subsequently introduced a twice-daily version, Wellbutrin SR, in 1996 and later, a once-daily version, Wellbutrin XL, in 2003. As can be seen in Figure 82, this strategy enabled GlaxoSmithKline to retain a significant portion of sales even post patent expiry.

Figure 82: Wellbutrin franchise retention via line extensions (TRx)



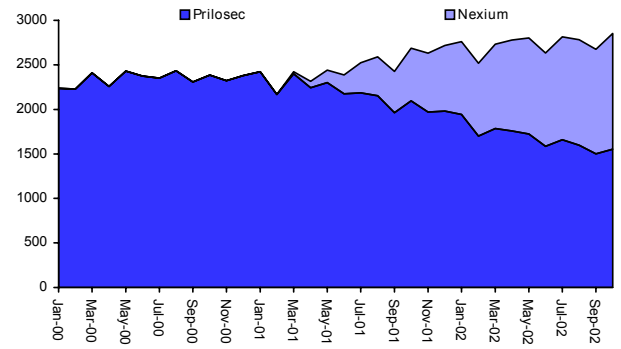
Source: IMS Health

- **Isomers**: Many molecules have two distinct forms which are mirror images of each other (called enantiomers). Although two forms are identical in formula and composition, one enantiomer may demonstrate a better 'fit' for the chemical receptor. This is much like a pair of human hands, where the right hand may fit a right glove better. In most instances, the pharmacological effect of the molecule rests with only one of the two forms. Hence, a formulation

containing only the chemically active enantiomer may potentially be more efficacious, or better tolerated than the original drug.

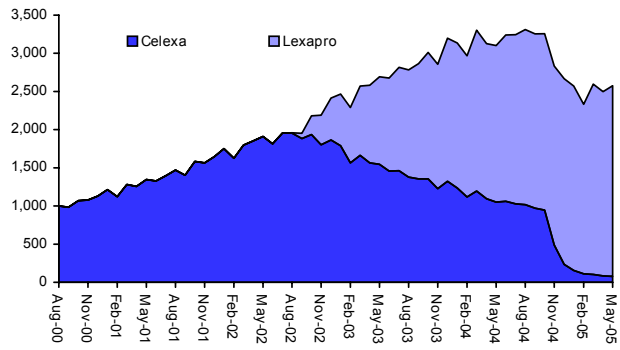
Several companies have seized upon this difference as an opportunity to develop and patent the more pharmacologically active form and market it as a new drug. For example, AstraZeneca's Nexium is a pure enantiomer of the older anti-ulcer drug Prilosec. Clarinex, Schering-Plough's follow-up to its leading anti-histamine, Claritin, and Forest/Lundbeck's Lexapro, a follow-on to its antidepressant Celexa, are all chemically active pure enantiomers of older blockbuster drugs. As 'new' molecules, these enantiomers were patent protected and help extend the life of the franchise. However, given the now 'obvious' need to select the active enantiomer for new R&D, extending the lifecycle by isomers is no longer a viable strategy in most instances.

Figure 83: Isomers as a means of protecting franchises – NRx Nexium and Prilosec



Source: IMS Health

Figure 84: Isomers as a means of protecting franchises – TRx Celexa and Lexapro



Source: IMS Health

- **Combinations**: Another effective means of extending the life of a successful drug is to develop a combination product which provides compliance and/or efficacy benefits, e.g. the patient need only take one drug once a day instead of two. An example is GlaxoSmithKline's asthma inhaler Seretide/Advair. By combining a long-acting beta agonist (salmeterol) with its steroid inhaler (fluticasone), patients need only use one inhaler instead of two. The combination patent expiring in September 2010 helped sustain sales of the aerosolised steroid, fluticasone proprionate, and the long-acting beta agonist, salmeterol, past beyond their respective patent expiries. In this case, GSK's complicated drug/device combination also provides significant protection.

Patents and market exclusivity

Introduction

As with any research-driven industry, the pharmaceutical sector can be economically viable only if the huge upfront investment required to innovate and develop new medicines results in a benefit to the innovator. For drug manufacturers, this benefit and, indeed, the incentive to continue to invest vast sums of money in research, depend vitally on a company's ability to patent its discoveries. By protecting intellectual property, patents provide research-based companies with a period of market exclusivity to recoup their investment and provide the capital for further innovation.

Patents

Following the GATT (General Agreement on Tariffs and Trade) accord in 1995, patent rights were recognized and harmonized internationally, and an international minimum standard patent term length was established. This was fixed at 20 years from the date on which the patent application was filed with the relevant authority, for example, the European Patent Office in Europe, the US Patent and Trademark Office or the Japanese Patent Office. In the US, patent details for pharmaceutical drugs may be found in the FDA's Orange Book, which is available online.

Most pharmaceutical companies file a number of patents on a unique compound as they seek to ensure that their discovery is fully protected from imitation. For a patent to be listed in the Orange Book and therefore fall under the auspices of Hatch-Waxman legislation (see later), the innovator company must notify the FDA of the issuance of a patent by the PTO within 30 days. While certain patents cannot be listed in the Orange Book (among other things, those surrounding a metabolite, tableting or a manufacturing process), several are key:

- **Composition of matter**: This represents the basic patent on the new chemical entity and its molecular structure. Composition of matter patents typically afford companies the greatest protection and are least likely to be successfully challenged. Generic manufacturers will typically seek to launch copy products following the expiry of this patent.
- **Method of use**: A method of use patent seeks to protect the indication for which the compound is used. Recent patent disputes suggest that method of use (or mechanism of action) patents are increasingly difficult to uphold, but they often provide delays to generics through time consuming litigation.
- **Formulation**: Formulation patents cover the form of delivery developed by the innovator company to enable the drug to be absorbed by the body, reach the relevant organs and release the active drug according to a desired concentration profile. Several types of formulation patents may be issued throughout the drug's market life as the drug innovator develops new ways to deliver its products. Formulation changes and patents typically represent a key feature of lifecycle management as pharmaceutical companies attempt to extend usage of the branded drug after the expiry of its composition of matter patent.

Market exclusivity

While the initial patent life on a new molecular entity usually runs for 20 years from the date of filing, the period between filing and market launch is invariably a matter of several years, as the pre-clinical, clinical and approval periods eat into any new

molecules' patent life. As such, we estimate that, on average, when a new molecule eventually obtains marketing approval, it usually has little more than 10 years of patent protection remaining.

However, in certain instances, the clinical and regulatory processes can take so long that, by the time it is approved, a new drug will have little, if any, patent life remaining. Such a scenario can hardly be seen to favour the innovator. With this in mind, legislation has been drafted in both the US and Europe that affords drugs periods of market exclusivity on the basis of data presented to the regulatory authorities. Two pieces of legislation are key:

- **1984 Drug Price Competition and Patent Term Restoration Act (The 'Hatch-Waxman' Act)**. Under this law, a five-year period of data exclusivity for innovator products was instituted. This means that applications for generic copies of drugs cannot be submitted until five years after an innovator product has been approved for marketing by the FDA. This period of data exclusivity may run in parallel with a drug's patent life or beyond, whichever ends later. This helps to ensure that the innovator obtains at least five years of market exclusivity. The Act also outlines a pathway by which generic drug manufacturers may file an Abbreviated New Drug Application (ANDA) for approval of the generic drug (see next section). Given that ANDAs may require a year for approval and cannot be submitted until the five-year exclusivity period has expired (unless a non-infringement certification has been made, in which case the ANDA may be submitted after four years), the branded drug's exclusive time on the market may be closer to seven years (assuming that the branded company files suit against the generic and is awarded a 30-month stay, see later). In addition, new indications for approved products are entitled to a further three years of exclusivity in that indication (although if generics become available at the same doses for other indications, this affords little protection). Note that generic filings can be submitted against the additional three-year exclusivity at any time.

  Approved generic drugs each have an associated two-letter code. The first letter indicates equivalence to the original drug, with an 'A' rating indicating therapeutic equivalence and may be substituted in place of the original by the pharmacist without consultation with the physician. If the first letter is a 'B' rating, this indicates that there are potential/actual issues with absolute bioequivalence, and may not be substituted for the original drug. The second letter provides additional information about the drug, e.g. dosage form. Most generic producers aim to have their drugs receive at least an 'AB' rating, which is the minimum required for generic substitution.

- **The EU Directive relating to medicinal products**: This piece of European legislation creates non-patent-related marketing exclusivity for medicinal products in Europe comparable to that of Hatch-Waxman, but allows for a maximum period of ten years rather than five. No generic applications may be filed for the first eight years, and none may be approved over the subsequent two years. An additional year of market exclusivity is permitted for a new indication, if it is filed within the first eight years of exclusivity, and represents a significant benefit over extant therapy.

Patent term extensions

In addition, in the US, under the Hatch-Waxman legislation, in certain instances, patent-term extensions may be available for the active ingredient in a drug if the date of first marketing of the drug was delayed as a result of the regulatory review. For new drugs,

the regulatory period is defined as one-half of the term starting on the date on which the Investigational New Drug (IND) license is granted (so permitting the start of clinical trials) and ending on the date on which a request for marketing approval is filed, plus the entire period for which the marketing approval is pending. However, any extension given is limited to no more than five years and must not extend the marketing life of the product to over 14 years. A petition for the extension must be made within 60 days of marketing approval.

Hatch-Waxman and ANDAs (US only)

As a quid pro quo for patent life extension in the US, the 1984 Hatch-Waxman legislation established a procedure which simplified the approval process for generic drugs. In particular, the Hatch-Waxman Act established the procedure for Abbreviated New Drug Applications (ANDA) under which a generic drug may file for FDA approval. In short, once the innovator's patent and market exclusivity has expired, the generic manufacturer may use the safety and efficacy data of the innovator (hence, expiry of period of data exclusivity), and is only required to demonstrate that its product is 'bioequivalent' to the innovator drug. It then needs to certify to the FDA that the original innovator patent has expired, will expire on a particular date, was invalid or will not be infringed when it launches its version of the drug. Under Section 505(b)(II) Paragraph (IV) of the Act, it was also obliged to notify the patent holder of its intent to launch the drug if, at the time of launch, an Orange Book-listed patent was still in force.

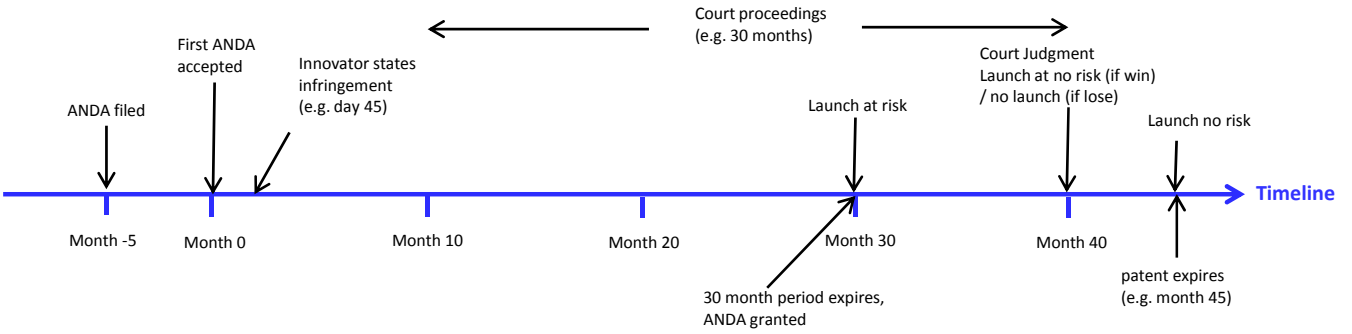
In practice, the workings of the Act are somewhat more complicated than it might at first appear. This is due to two main features: litigation and market exclusivity.

Litigation

Most innovator companies will seek to extend the patent life of their products and prevent the introduction of generics. As such, they will invariably allege that one of their many other (remaining) patents is infringed. Typically, this will be a formulation patent, or method of use patent. Having received a Paragraph IV notification, the innovator company has 45 days to file a suit alleging patent infringement. Should it fail to do so, no subsequent claim can be made and the FDA will assess and approve the application as per normal.

Assuming the innovator company files for patent infringement, the Hatch-Waxman Act prohibits the FDA from granting an ANDA until either the cessation of legal proceedings, which confirm patent invalidity, or 30 months, whichever is earlier. If the generic drug review is completed before either of these points in time is reached, its approval will be deemed tentative, full approval coming once 30 months have passed or a court decision has been reached. Once full approval has been received, the generic company is free to market its generic version once the unchallenged patent or patents (typically composition of matter) have expired. However, it should be noted that it does so in the knowledge that should the court proceedings find against it, it would potentially be liable for up to three times the losses suffered by the innovator firm (including punitive damages). This process is illustrated by the schematic shown below. (A more comprehensive overview of the US legal process is provided in the chapter on 'US patent litigation').

Figure 85: Illustrative timelines associated with Paragraph IV filings



Source: Deutsche Bank

Generic market exclusivity

In order to encourage the growth of the generics industry and give generic companies an incentive to enter the market at the earliest possible opportunity, the original Hatch-Waxman amendments also included provisions permitting 180 days of marketing exclusivity for the generic manufacturer that is the 'first to file' a complete ANDA with the FDA. Given the intense price competition that invariably follows patent expiration of a large branded drug, this provision is of considerable value to the generic manufacturer, allowing it to garner significant market share at a more favourable price than would be the case were all generic manufacturers to launch simultaneously. Until late 2002, the FDA granted this exclusivity to the first generic to file a complete and acceptable ANDA. However, following the precedent in 2002 with Prilosec, the FDA modified the original rules such that market exclusivity is now granted to the first manufacturer to successfully challenge the innovator patent, rather than just to the first company to file a complete ANDA (hence, prevent collusion and abuse of the system).

As to when this exclusivity commences, following several court rulings, the FDA announced in early 2000 that it would interpret the phrase 'ruling of the court' used in the 1984 legislation as being the 'ruling of the first court', i.e. the decision from the District (lower) Court. Thus, for Paragraph IV filings made after March 2000, exclusivity commences from the earlier of first marketing or a ruling of the first court (this assumes, of course, that the ANDA has been approved). This contrasts with the agencies' earlier interpretation that exclusivity would not commence until the earlier of first marketing or the decision of the final or appeals court.

Orange Book abuse

On several occasions, innovator companies have received and then listed in the Orange Book patents which were issued by the US PTO after an initial Paragraph IV notification had been filed. Having done so, the innovator company would then typically claim that this new patent was also being infringed. Applying its then interpretation of the 1984 Act, the FDA would subsequently enforce a further 30-month period before granting a marketing license to the ANDA filer (assuming no court ruling). Following several high profile cases, an FTC investigation into the matter led to an FDA pronouncement that only one 30-month stay would be permissible per ANDA filing.

Paediatric extensions

In order to encourage pharmaceutical companies to undertake studies on drugs with potentially meaningful health benefits in children, the Food and Drug Administration Modernisation Act of 1997 (FDAMA) included legislation which afforded companies a six-month exclusivity/patent extension if they submitted data relating to the use of an active drug in a paediatric population. Paediatric studies are defined as at least one clinical investigation in paediatric groups in which a drug is anticipated to be used. The extension is available only for products for which the FDA makes a 'Written Request,' which may be made at the behest of an interested party or at the FDA's own initiative. Trials must be conducted in accordance with the FDA's guidelines, but, assuming the data submitted meets the FDA's request, an additional six months of product exclusivity will be granted. Each 'Written Request' may result in only one period of paediatric exclusivity.

In January 2007, the European Medicines Agency passed a similar paediatric regulation where drug companies are required to submit a paediatric investigation plan (PIP) with their marketing authorization applications (unless children are not a target segment, in which case a waiver may be requested). New drugs with their PIP approved will receive a six-month patent extension, similar to the US. Manufacturers of off-patent drugs with an approved paediatric use marketing authorization (PUMA) may obtain 10 years of data protection, while orphan drugs will receive 12 years.

Orphan drugs

In order to encourage research in the area of rare diseases, legislation in the US, Europe and Japan has been passed for drugs used to treat these diseases. By offering market exclusivity and various tax breaks, health authorities have sought to encourage the industry to undertake research into disease areas that, because of their limited incidence and revenue prospects, may otherwise present limited commercial appeal.

The first territory to adopt orphan dug legislation was the US, which in 1983 enacted the Orphan Drug Act. This legislation has subsequently served as a prototype for a programme adopted in Japan in 1993 and the European Commission in 2000. In 2007, the FDA and EMA agreed to adopt a common application process for both agencies, though the approval process will remain separate.

In the US, an orphan disease is defined as either one which affects under 200,000 patients or one which would not recoup development costs on the basis of US sales. Overall, 10-20 million Americans suffer from approximately 5,000 or so orphan diseases for which there are no available cures, such as Huntington's disease, Fabry disease and many genetic disorders. To help these patients, the law provides two principal incentives to make it commercially feasible to develop orphan drugs – a seven-year period of market exclusivity (compared to the normal five years) and a 50% tax credit for certain clinical research expenses incurred in development. In addition, orphan drugs often receive fast-track approval status.

In Europe, an orphan disease is defined as a life-threatening or chronic disease that has an incidence of less than five in 10,000. Companies developing such drugs are exempt from some or all of the licensing fees, and will be granted exclusivity for up to ten years. In 2010, in a ten-year review of the orphan drug program, EMA reports that it has received 1,113 applications for orphan medicine designation, with 724 medicines granted orphan status by the European Commission. It has received 114 marketing authorization applications for orphan-designated medicines and 62 have received approvals.

Figure 86: Summary of key FDA exclusivity types

Code	Definition	How long	Examples
NC	New combination	3 years*	Symbyax (Prozac + Zyprexa), Caduet (Norvasc + Lipitor)
NCE	New chemical entity	5 years	Iressa, Levitra, Eloxatin
NDF	New dosage form	3 years*	Zomig ZMT
NE	New ester or salt of active ingredient	5 years*	Valcyte (new ester of Cytovene), Lexiva (pro-drug of Agenerase)
NP	New product	3 years*	Nexium (single isomer of Prilosec)
ODE	Orphan drug exclusivity	7 years	Copaxone (multiple sclerosis), Gleevec (gastrointestinal stromal tumours)
PED	Paediatric exclusivity	6 months	Cipro, Nexium, Epivir

Source: Source: FDA, Deutsche Bank estimates
**Only granted if new product approval is based on results of new clinical investigations, not including bioavailability studies.*

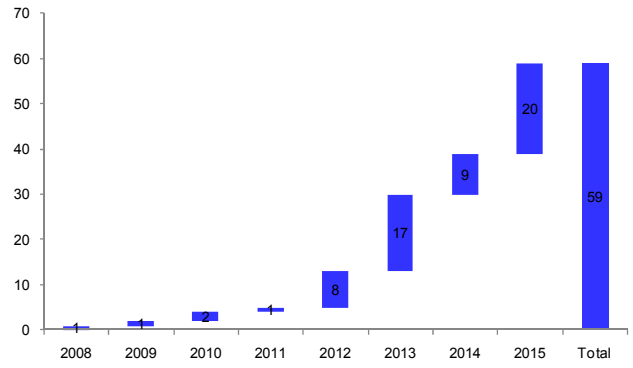
Biosimilars

A $60 billion sales opportunity by 2015E

The issue of biosimilars (generic copies of biological products) is a much more complex issue than generic copies of a chemical pill. While the biologic market has seen little meaningful generic competition to date (with the exception of certain therapeutic proteins such as erythropoietin, G-CSF and human growth hormone in Europe), this is due in no small part to unanswered questions surrounding regulatory standards required in order to demonstrate bioequivalence/similarity to the original product. Compounding this are the barriers to entry provided by the heavy capital investment requirements (biologics are much more complex, time-consuming and expensive to manufacture than traditional oral or injectable medicines) and the hefty R&D costs (where guidelines are in place, these require moderately sized clinical trials versus the originator product).

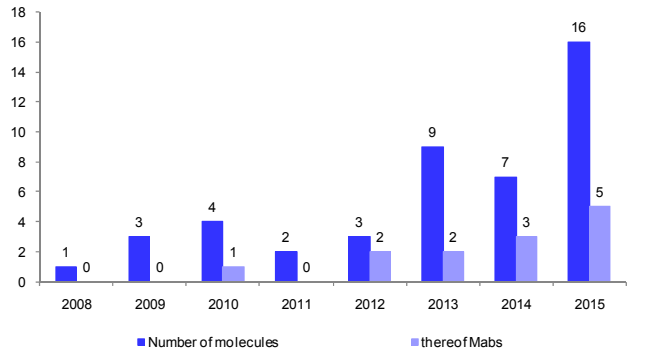
There are therefore significant questions over how much of a threat biosimilars ultimately will represent to the branded companies, given manufacturing complexity and associated barriers to entry. However, the potential opportunity is large (c.$60 billion of biologics sales will be subject to patent expiry by 2015) and several larger players are investing heavily, notably the generic leaders, Teva and Sandoz (Novartis). We expect current draft regulatory guidelines to be formalised over 2012/2013 clarify the requirements (first biosimilar guidelines in the US, guidelines for monoclonal antibodies in the EU). Figure 87 and Figure 88 illustrate the market opportunity for biosimilars, which arises principally from 2013 onwards.

Figure 87: Sales exposed to patent loss by year $bn



Source: Lonza IR presentation

Figure 88: Patent expiry of biologic compounds



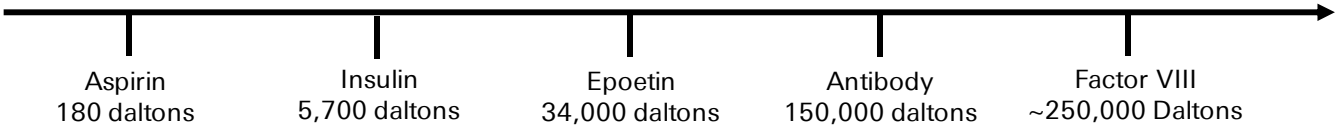
Source: Lonza IR presentation

Question of complexity

Biologic products such as monoclonal antibodies, or proteins, are not manufactured by a chemical process, but are instead produced by living organisms such as cells (human, yeast or animal) or bacteria, through the insertion of new DNA encoding for the required biological protein into the cells' own DNA. After the protein is produced within the cell, it may be further modified by other processes within the cell (e.g., adding chains of amino acids and sugars, having different folding configurations). These processes may be unique to the cell type chosen, the method of cell cultivation,

purification process etc. Figure 89 provides a illustrative diagram of the size of different biologic products as compared a small molecule such as aspirin.

Figure 89: Biologics vary in size and complexity



Source: Bloomberg Biosimilars Symposium

With the increasing size comes increasing complexity. This is because in addition to the molecular structure, other factors such as the configuration (folding of the molecule) and attachment of sugar side-chains (glycosylation) play important roles affecting the products' efficacy, immunogenicity and clinical profile. These latter two factors may vary according to the organism used to produce the product, and the conditions under which they are grown. Hence, unlike small molecule drugs, the production process itself plays an important role in determining the characteristics of the biologic product, making the process of producing and proving bioequivalence much less simple or straightforward. Thus regulators cannot be sure a product is equivalent without human trials.

Sales opportunity may not equate to profits

While the potential opportunity appears large at first glance, (patents for products with c.$60 billion of sales expiring 2015E), the true opportunity for biosimilars may not be what it first appears. Due to the higher hurdle to demonstrate bioequivalence for regulatory approval, the R&D expense may be in the order of several hundred million dollars, many orders of magnitude higher than the <$10 million required for small molecule generics. The high level of technological expertise required will also narrow the opportunity to a handful of companies. Given the much less intense level of competition, we do not expect a similar rate of price erosion or market share loss as for generic small molecules (generics priced at 80-90% discount, leading to loss of market share of 80-90% in first year). However, the cost of manufacturing a biologic product is also higher than for small molecules, so margins are still likely to be thin in the absence of significant volume.

The competitive dynamics in the European markets, which have seen the approval of several rudimentary biosimilar compounds make for an interesting case study. We note that penetration of biosimilars in Europe has started to become meaningful after a slow start. G-CSF biosimilars (approved September 2008 onwards) took around a 20% market share after 30 months, as compared with 10% for the earlier launched EPO biosimilars (approved August 2007 onwards). Furthermore the market share of biosimilar EPO (EPO alpha) now has reached almost 70% in Germany and G-CSF over 40%. Interestingly this has not been prompted by very intense price competition (albeit some competition is evident) as the current discount of European EPO biosimilars to the branded equivalents is around 14%, as compared with 17% at launch. However, this is on a background of originator prices falling 21% from September 2008 to June 2012. Hence, while the opportunity available to biosimilars appears attractive over the next few years, the profit opportunity could be smaller than headline numbers suggest.

EU regulation now encompasses monoclonal antibodies

As discussed, Europe has an established pathway for the approval of biosimilars and has approved biosimilars of several therapeutic proteins. In 2010, the regulatory body (EMA) issued draft guidance to industry covering biosimilar requirements for monoclonal antibodies. Although the guidelines require non-inferiority clinical trials (which could limit the number of competitors due to the cost involved), they allow the use of surrogate markers (on a case by case basis) to prove efficacy and safety (meaning shorter and cheaper trials are possible than for the original approval of new biologic drugs). Furthermore, extrapolation of efficacy and safety from one indication to other similar indications is possible. The EMA is reviewing an application for biosimilar Remicade (infliximab) from Korean firm, Celltrion, representing the first monoclonal antibody biosimilar to be submitted to the EMA.

Looking ahead, we await new guidance on previously off-the-table drug classes (revised consultation papers were released during 2011), including enoxaparin (generic blood thinner Lovenox) and modern insulins (risks to Sanofi, Eli Lilly and Novo Nordisk respectively). In the case of the former the EMA is exploring the possibility of replacing its previous guidance of requiring a clinical efficacy trial with the possibility of substituting this with physiochemical characterisation data (eg. Laboratory tests, as used for the drug's FDA approval in the US). In the case of the latter, the EMA is expanding guidance to include considerations for insulin analogues (both long and short acting) which were excluded from previous guidance.

FDA must propose a biosimilar pathway by 2012

The US is some way behind Europe in establishing guidelines but the process is now underway. The Biologics Price Competition and Innovation Act (a component of Obama's Patient Protection and Affordable Care Act) mandates the presentation to Congress in 2012 of a proposed approval pathway for biosimilar applications (called 351(k)), and will be enacted as part of the Prescription Drug User Fee Act (PDUFA) renewal for 2013-2017.. For branded drug manufacturers, in return, they have been granted 12 years of data exclusivity for biologic substances. The Act mandates that the FDA may review biosimilar applications only after at least four years after the approval of the original compound and also provides for an exclusivity period for the first approved interchangeable biosimilar product.

In anticipation of its presentation to Congress at the end of 2012, the FDA released draft guidelines in March 2012 for manufacturers seeking to use this new pathway for the regulatory approval of biosimilar products. The FDA intends to use a 'totality of evidence approach' to the assessment of applications. Our interpretation is that the FDA will look at each product on a case by case basis, assessing the totality of evidence, requiring clinical studies but allowing for state-of-the-art analytics to reduce the scope of these, and with inter-changeability (substitution at the pharmacist level) a possibility. Biosimilars will in most cases be required to conduct human pharmacokinetics and pharmacodynamics studies, including demonstrating a similar "clinical safety and effectiveness" with the original product, which we believe will involve the conduct of a clinical trial of a reasonable size.

We expect the key political debate points to centre around the duration of exclusivity for reference products (currently 12 years, potentially reduced to 7 years) and the daunting prospect of handing over a full dossier of clinical/ manufacturing information to the originator company (currently the prospect means many would-be biosimilar

companies are dissuaded from submission due to allowing the originator to prepare patent defence arguments and handing over proprietary know-how to the competition).

Biosimilar insulin a lesser threat than monoclonal antibodies

The majority of Novo Nordisk's exposure (and that of Sanofi) comes from patent expiries of insulin and insulin analogues, which we view as a less attractive opportunity for biosimilars than monoclonal antibodies (as exemplified by Sandoz indicating that it will not enter the insulin space). While the technological hurdles to produce recombinant insulins are lower, the production volumes required are huge (dwarfing those of monoclonal antibodies), necessitating very heavy capital investment (industry discussions suggest $0.5-$1 billion to produce a meaningful global supply). Furthermore selling prices (and thus EBIT margins) are relatively low. A diabetes primary care sales force is also likely required in a number of markets. Together, these factors entail large economies of scale and upfront investment, thereby favouring the incumbent insulin manufacturers. Furthermore, in the Emerging Markets, where generics are generally available, brands are usually more trusted and thus retain the lion's share of the market (e.g. Novo's share of the Chinese insulin market is c.60% despite competition from numerous local manufacturers and from MNCs).

It was therefore noteworthy to us that, in Pfizer's previous deal (announced October 2010) to sell generic insulin supplied by the Indian manufacturer Biocon, the timelines presented for launch in the major markets were relatively distant and Pfizer's investment was relatively limited (suggesting uncertainties on its part). The deal was eventually called off in March 2012, citing "individual priorities" but we believe it highlights the difficulty firms will likely face in getting a biosimilar insulin approved. The insulin analogues such as insulin glargine (Lantus) represent a greater challenge still to biosimilar manufacturers, but the revision of EU guidance documents (as discussed above) could provide greater clarity on the threat during 2012. Lilly is attempting to develop a generic version of Lantus through its diabetes partnership with Boehringer Ingelheim and likely represents the greatest threat to Sanofi as it already has the economies of scale and sales forces referenced above.

Biosimilar monoclonal antibodies still the focus for companies

Unsurprisingly the past year has seen confirmation that a number of companies, notably Teva (via its collaboration with Lonza) and Sandoz are working on biosimilars of monoclonal antibodies (including cancer drugs Herceptin and Rituxan) and have started late stage comparative clinical trials of their molecules (note: the EU patent on Rituxan expires in November 2013). Amgen and Watson have also agreed to collaborate to develop and sell biosimilar versions of monoclonal cancer drugs under a joint label. Outside of these main players, the US-based Hospira has a collaboration underway with the South Korean company, Celltrion, to develop a portfolio of biosimilars, including versions of Remicade (which has been submitted to the EMA), Herceptin and Rituxan. These companies have aspirations to file and launch Herceptin in the near-term in Asian markets. Other partnerships of note in the space include: Stada and Richter's partnership to develop generic Rituxan and Herceptin (albeit this has the less than ambitious target of bringing the product to the market by 2017); Biogen Idec's partnership with Korean manufacturer Samsung to produce biosimilars except of those products made by Biogen; and Fujifilm's joint venture with Kyowa Hakko Kirin, which aims to commence trials for its first drug candidate in 2013.

US patent litigation

Legal standards for patentability

Given the high frequency of patent challenges in the pharmaceutical sector, we have provided in this section an overview of key US patent legislation and the litigation process in order to provide a framework with which to understand and follow the progression of ongoing lawsuits.

The US Patent and Trademark Office defines a patent as "the right to exclude others from making, using, offering for sale, or selling" the invention in the United States, or importing the invention into the United States for a limited time (currently 20 years in most cases). According to US patent law, in order for an invention to be patentable, it must be both novel and non-obvious. These requirements are set forth in Title 35 of the United States Code (USC), Sections 102 and 103. (Figure 90)

Novelty

In order for a patented product to be considered novel, it must not have been previously described in a form of prior art. Prior art is defined under Section 102(a) and (b) of the statute as public knowledge that was known and available before invention by the patentee. Section 102(d) places emphasis on the timing of a patent filing and requires that the patentee file an application within one year of describing the invention in a written publication.

In legal terms, a patent claim is said to be 'anticipated' if the claimed invention is found to be substantially the same as that described in a prior art reference. Determination of anticipation requires a two-step analysis:

a) Claim construction of the challenged claims (a question of law), and

b) Determination of whether a single prior art reference contains each and every element of the challenge claims (a question of fact).

What is important is that the standard for proving anticipation is rigorous and if a court must look beyond a single prior art reference (considering both specific and inherent claims), the proper legal challenge should be obviousness, not anticipation. In addition, the prior art reference must be 'enabling', that is, it must contain 'a substantial representation of the patented improvement in such full, clear and exact terms as to enable any person skilled in the art or science to which it appertains to make, construct and practice the invention to the same practical extent as they would be enabled to do if the information was derived from a prior patent'. Seymour v. Osborne, 78 U.S. (11 Wall). 516, 20 L.Ed.33 (1870).

Non-obviousness

The second key element required for patenting is non-obviousness. According to 35 USC 103, "if the differences between the invention and the prior art are such that the invention would have been obvious at the time it was invented to a person having ordinary skill in the art", then it would be considered obvious and would not be patentable.

The original test for obviousness was set forth in a Supreme Court decision, Graham v. John Deere Co., 383 U.S. 1 (1966), in which the Court required consideration of three factors:

a. The scope and content of prior art,

b. The differences between the prior art and the claims at issue, and

c. The level of ordinary skill in the pertinent art.

Subsequent litigation in the Federal Circuit Court, B.F. Goodrich Co. v. Aircraft Braking Systems Corp., 72 F.3d 1577, 1582 (Fed.Cir.1996) and Hybritech, Inc. v. Monoclonal Antibodies, Inc. 802 F.2d 1367 (Fed. Cir. 1986) expanded this definition to include a fourth factor:

d. Secondary considerations, if any, of non-obviousness, which may include but are not limited to: 1) the commercial success of the invention, 2) whether the invention satisfied a long-felt need in the industry, 3) failure of others to find a solution to the problem at hand, and 4) unexpected results.

Again, it is important to note that there must be a motivation to combine the insights provided in the various prior art references in order to render an invention obvious. This 'reason, suggestion or motivation' must derive from the references themselves, knowledge of those skilled in the art, or 'the nature of the problem to be solved, leading inventors to look to references relating to possible solutions to that problem'. For example, in KSR International Co. v. Teleflex, Inc., 550 US 398 (2007), the courts elaborated the scope of what is obvious, making it easier to invalidate patents based on obvious combination, following an expansive and flexible analysis of non-obviousness. The court expanded on Graham's three-part framework to formulate the requirement of non-obviousness to a person having ordinary skill in the art (PHOSITA) having both good reason to create the invention in light of the prior art and a reasonable expectation of success in doing so.

Moreover, the courts have cautioned against using hindsight in making a finding of obviousness. In Rockwell Int'l Corp v. United States, 147 F.3d 1358, 47 USPQ2d 1027 (Fed. Cir. 1998), the court indicated that it was inappropriate to use the patent in suit 'as a guide through a maze of prior art references, combining the right references in the right way so as to achieve the results of the claims at suit.' In addition, the mere disclosure of a multitude of possibilities (e.g., a broad class of chemical compounds that may be useful in producing a desired therapeutic effect) but without a suggestion as to which of the possibilities is likely to be successful, should not invalidate a claimed invention simply because the inventor could have tried each of the numerous possibilities until he eventually arrived at a successful result.

Figure 90: US patent legislation – 35 USC 102 and 103

35 USC 102 (Novelty)
(a) A person shall be entitled to a patent unless – the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent.
(b) A person shall be entitled to a patent unless – the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.
35 USC 103 (Non-obviousness)
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
(b) (1) Notwithstanding subsection (a), and upon timely election by the applicant for patent to proceed under this subsection, a biotechnological process using or resulting in a composition of matter that is novel under section 102 and non-obvious under subsection (a) shall be considered non-obvious if –
(A) claims to the process and the composition of matter are contained in either the same application for patent or in separate applications having the same effective filing date; and
(B) the composition of matter, and the process at the time it was invented, were owned by the same person or subject to an obligation of assignment to the same person.
(2) A patent issued on a process under paragraph (1)
(A) shall also contain the claims to the composition of matter used in or made by that process, or
(B) shall, if such composition of matter is claimed in another patent, be set to expire on the same date as such other patent, notwithstanding section 154.
(3) For purposes of paragraph (1), the term ''biotechnological process'' means –
(A) a process of genetically altering or otherwise inducing a single- or multi-celled organism to – (i) express an exogenous nucleotide sequence, (ii) inhibit, eliminate, augment, or alter expression of an endogenous nucleotide sequence, or (iii) express a specific physiological characteristic not naturally associated with said organism;
(B) cell fusion procedures yielding a cell line that expresses a specific protein, such as a monoclonal antibody; and
(C) a method of using a product produced by a process defined by subparagraph (A) or (B), or a combination of subparagraphs (A) and (B).
(c) Subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person

Source: United States Code Title 35 - Patents

Inequitable conduct

Although there are other requirements set forth in US patent law, the most common avenues for patent challenges relate to prior art and obviousness. While a generic company could also challenge a patent, for example, by arguing that one of the original inventors was not named on the application under 35 USC 102 (f), such arguments are generally weak unless they are proven to be a result of willful misconduct on the part of the patentee.

That said, most parties wishing to challenge a patent's validity will argue that the patentee committed inequitable conduct by intentionally misleading the Patent Office. While such inequitable conduct claims are among the most difficult to prove, they are often included in litigation because the entire patent is rendered invalid if the patentee is found guilty. This is in contrast to arguments of anticipation or obviousness, which must be proven claim by claim.

In order for a court to find a patentee guilty of inequitable conduct, it must determine that the patentee misled the Patent Office by intentionally misrepresenting or omitting a fact that the reviewer would have considered material in his or her review. This requires a finding of both materiality and intent. However, because of the difficulty in proving both of these issues, findings of inequitable conduct are generally uncommon.

The US litigation process

Initial proceedings: The complaint and answer

When an innovator company wants to claim infringement of its patents, it files a 'complaint' with one of the Federal District Courts. (According to US law, the Federal District Courts have exclusive jurisdiction for all patent litigation). The complaint describes the company's alleged injury (patent infringement) and how the defendant caused the injury (filing of an Abbreviated New Drug Application [ANDA] with an intent to launch a generic version of the drug). It also makes a specific request for relief (e.g., an injunction preventing launch) and/or damages. This action triggers the 30-month Hatch-Waxman stay described in the previous section.

The generic firm must next file a reply in which it admits or denies the plaintiff's allegations. In addition, the defendant may assert 'counterclaims' in which it argues, for example, why the plaintiff's patents should be ruled invalid. It is important to note, however, that the pleading in the US federal courts is 'notice' pleading. This means that each party merely provides enough information in the complaint, answer and any counterclaim to put the other side on notice of its claims. More factual detail is gathered through the discovery process which follows.

In these early stages, the branded company may request a jury trial, as historical precedent suggests a greater probability of patents being upheld when considered by a jury versus judge. In most cases, however, the court will deny this request, leaving the presiding judge to render the decision. (Although the US Constitution guarantees the right to a jury trial, it requires that damages be in excess of $20. But as patent lawsuits usually precede the launch of generic products, at the time of trial there are typically no damages yet accrued).

Discovery

The next phase of litigation is the discovery process. During discovery, the litigants obtain information from one another through the use of depositions (testimony under oath), interrogatories (lists of pointed questions) and requests for documents. While some of these requests may raise concerns over the disclosure of proprietary information, trade secrets, etc., each party is required to provide such information if it is admissible in court or is likely to lead to admissible evidence. However, there may be interim disputes which may require the court to intervene when one party refuses to disclose information to the other.

Discovery is the most time-consuming and expensive part of the litigation process, and usually takes many months, if not years. For example, in the patent litigation surrounding Sanofi's Plavix, discovery was not complete until some 18 months after the case was initially filed.

Claims construction (the Markman hearing)

A key element of patent litigation is the claims construction hearing. During the claims construction process, the court will rule on the interpretation, and thus the scope, of the patent claims. For example, regarding the claim in Sanofi's '265 patent for Plavix describes a dextro-rotatory isomer 'substantially separated' from the levo-rotatory isomer, the court might specify what percentage purity is implied by the phrase 'substantially separated'.

In making its decision, the court considers the written patent description and drawings along with the patent prosecution history. In addition, the court may consider 'extrinsic' evidence (i.e., information not specifically described in the patent documentation) if

necessary, to help the court understand the underlying technology or to find the ordinary meaning of a disputed term. However, the focus must remain on the meaning of the claim language itself, and extrinsic evidence cannot be used to explain away ambiguity or vary the claim terms. As stated in the Markman opinion, 'the invention protected by the patent must be covered by the claims; otherwise it is lost.'

Summary judgment

Following the claims construction hearing, either of the litigants may file a motion for summary judgment with the court. A motion for summary judgment asserts that there is no 'genuine issue as to any material fact' and that the moving party is entitled to judgment as a 'matter of law.' Anderson v. Liberty Lobby, 477 US.242 (1986). That is, the moving party will argue there is no need for a trial because the facts (including those gathered in discovery, the pleadings and any affidavits) are not in dispute between the two parties.

In pharmaceutical patent cases, it is generally the generic company which files the motion. In contrast, the branded company is typically content to let the legal process – and thus the continued freedom from generic competition – drag on for as long as possible. For a drug with significant sales, the cost of a few additional months of legal fees is typically less than the potential profits that would be lost if there were an early generic launch.

Resolution of a summary judgment motion is rarely a straightforward determination, however, and both parties submit briefs explaining why they believe there are or are not outstanding questions of fact that should be left for consideration at trial. In addition, because there are often multiple issues involved, it is not uncommon for a judge to grant summary judgment on some claims but not on others.

Pre-trial hearing and order

The next stage in the litigation process (assuming the case has not been decided by summary judgment) is the pre-trial hearing, during which the judge and attorneys meet to plan the framework of the trial. The court will subsequently issue a pre-trial order confirming the matters addressed in the pre-trial conference, which may include the nature of the case, the theories of the parties, the admitted facts, the facts in dispute and the list of witnesses and exhibits to be introduced at trial. In addition, the court set the trial schedule at this time.

The trial

About one to three years after the start of litigation, the case will come to trial. If the case is heard by a jury, the verdict will be rendered at the end of the trial. After a bench trial, however, the parties may, either on their own initiative or at the request of the court, submit post-trial briefs in which they argue for a set of findings of fact and conclusions of law which they want the court to adopt. Thereafter, the court may deliberate for several weeks or months before issuing its written opinion.

The appeals process

If either party is unsatisfied with the District Court's verdict, it may appeal the case to one of the 12 regional Courts of Appeals or to the Federal Circuit Court of Appeals. The 'appellant' (the party appealing the decision) must initiate the appeal within 30 days of the lower court decision by filing a Notice of Appeal with the District Court. Thereafter, the appealing party will submit a written brief in which it argues that the lower court erred in its decision. The other party, the 'appellee', will respond with a similar brief and may, if it was displeased with certain parts of the decision, elect to cross-appeal. The appellant then files a final reply brief with the court.

Appeals cases are heard by a panel of three judges (who are often better-versed in patent litigation than the District Court judges). The panel will have received a copy of the parties' briefs and will subsequently hear short (15-30 minutes on average) oral arguments from each of the litigants.

It is important to emphasise that the authority of the appellate court is limited. The court is not permitted to receive new evidence or hear witnesses, but instead, relies upon the factual findings of the lower court and the transcript of the trial. It can only overturn these findings if they are determined to be 'clearly erroneous,' meaning that a reasonable person could not reach the factual conclusion of the lower court based on the evidence presented at trial.

Instead, the primary focus of the appellate court is on questions of law and whether the lower court correctly applied the law. If it determines that the lower court erred in its application, it can decide to reverse the lower court's decision. However, if the application of the law involves a judgment because the law itself is unclear, the appellate court may not substitute its judgment for that of the lower court.

Many months may pass before the Court of Appeals issues a decision. This decision may simply be an affirmation or reversal of the original verdict, or it may include a request that the case return to the lower court for resolution of some matter (for example, if a District Court granted a preliminary injunction preventing a generic company from launching its product and the appellate court overturned the injunction, the patent case would return to the lower court for further litigation). Note that the decision by the Court of Appeals is binding on the parties, and to the extent it decides new legal premises, is binding on parties within that Circuit.

Finally, a litigant dissatisfied with the appellate decision may file a petition for a 'writ of certiorari' – a document asking the US Supreme Court to review the case. The initiating party, now known as the 'petitioner', files a brief supporting its request for review and the opposing party, the 'respondent', files a brief opposing review. If the petition for certiorari is granted, the parties will file briefs similar to those filed in the Court of Appeals.

Review by the Supreme Court is discretionary, and is granted for only a fraction of cases that involve an unusually important legal principle, or when two or more federal appellate courts have interpreted a law differently. If review is granted, the parties will file further briefs and argue their case before the nine Supreme Court justices. The Court will subsequently issue a written decision. This decision becomes the 'law of the land' and is binding on the parties and all other persons.

US legislative process

Law-making in the United States

Given the importance to the pharmaceutical industry of the changing US legislative landscape, we thought it useful to include a brief description of the US legislative process. This may, for example, help readers follow the progress of any medical reform legislation in this and future sessions of Congress.

The process for a bill to become law in the US is often a long and complicated process, replete with procedural rules and loopholes. According to the US Constitution, legislative responsibility falls to Congress. The US Congress is divided into two separate but equal bodies, the House of Representatives (or House, for short) and the Senate. The House comprises 435 members, elected every two years. The Representatives are apportioned to the populations of each of the 50 states. The Senate comprises 100 members – two from each state, with the Vice President voting in the event of a tie. Senators are elected to terms of six years, with one-third of the total membership of the Senate elected every other year. Each 'Congress' lasts two years and is divided into a First and Second session. The 112th Congress began its term in January 2011.

Figure 91: Composition of 112th US Congress (2011-13)

House of Representatives*	Senate
242 Republicans	51 Democrats
190 Democrats	47 Republicans
3 vacancies	2 Independent

Source: US House of Representatives, US Senate

Types of legislation

Ideas for new legislation may arise from a variety of sources – from the members of Congress, from individuals or citizen groups, from a member of the President's Cabinet or from the President himself. Once an idea is conceived, a member of Congress must propose the draft legislation into his or her respective house.

There are four principal forms of legislation: the bill, the joint resolution, the concurrent resolution and the simple resolution. The most common of these is the bill, which may be introduced in either the House or the Senate. The exceptions to this are bills for the raising of revenue, which must originate in the House. By tradition, general appropriation bills also originate in the House. Bills may be 'public,' affecting the general population, or 'private,' affecting a specific individual or private entity. The term 'companion bill' is also used to describe a bill introduced by one chamber of Congress that is similar or identical to a bill under consideration by the other chamber. In the 111th Congress, a total of 6,562 House bills and 4,059 Senate bills were introduced.

Though there is no practical difference in laws passed by a joint resolution and a bill, they are generally used for different purposes. Like a bill, a joint resolution may be introduced in the House or the Senate but not jointly in both houses, as often assumed. It is subject to the same approval procedure as bills, except they must be passed in both chambers in the same form. The exception is a resolution proposing a constitutional amendment, in which case, the resolution must be approved by two-thirds of the House and the Senate and ratified by three-quarters of the states. This is not reviewed by the President.

Concurrent and simple resolutions are used for regulating the operations of one or both houses. Concurrent resolutions affect the operations of both houses, whereas simple resolutions affect only the House or the Senate. To be effective, each resolution must be approved only by the relevant house(s).

Introduction and referral to committee

For the purpose of simplicity, we will focus on the legislative pathway for a bill introduced in the House, as the process is similar for a bill originating in the Senate. Any member or group of members may introduce a new bill or joint resolution. Upon introduction, the bill is referred to the appropriate committee with jurisdiction over its subject matter. This is perhaps the most important phase of the legislative process, as the committees hold primary responsibility for scrutinising the bill. In fact, only a small percentage of bills ever make it past their relevant committee.

Currently, there are 21 standing committees in the House and 16 in the Senate, in addition to several joint, select and special committees. Each committee is further broken down into subcommittees. Healthcare matters fall under the jurisdiction of the Committee on Energy and Commerce in the House of Representatives and the Committee on Health, Education, Labour and Pensions in the Senate.

Membership of committees is divided between the two major political parties. By custom, the division approximately reflects the split in the house as a whole. Each of the two parties initially assigns its members to committees, with the final slate being approved by the full chamber. Each committee also elects as chairman a member of the majority party.

During the review process, the subcommittee solicits opinions from the relevant government agencies and non-government experts. The bill is then amended during a so-called 'mark-up' session, after which the subcommittee may decide to report a favourable, an unfavourable or no recommendation to the parent committee. A similar process follows in the full committee. However, the parent committee may also vote on the measure and forward it to the whole House.

Motion to discharge committee

Occasionally, the committee process may be circumvented by what is known as a 'discharge petition.' If a bill has been held up by a committee for at least 30 days, or if the Committee on Rules refuses to clear it for floor action within seven days, any member may offer a motion to discharge the committee from the bill. A simple majority is required to pass the motion. While discharge petitions are seldom successful – members are reluctant to disregard the committee judgement and review process – the threat of such a move may spur a committee to act.

Committee recommendation to the House

If the committee votes to report the bill to the House, it drafts a report describing the purpose and scope of the bill and the reasons for approval. The report will highlight any areas of existing law the bill proposes to change. It will also state all amendments to the original draft. (These reports often serve as the most valuable resource in understanding the history of a law and are frequently referenced by courts and executives).

When a public bill is favourably reported to the House, it is assigned a calendar number on the Union or House Calendar. The Union Calendar includes all public bills regarding the raising of revenue or the appropriation of money or property. All other public matters are scheduled on the House Calendar.

All measures on the Union Calendar must first be considered by the Committee of the Whole House, an abbreviated version of the full House that requires only 100 members for a quorum. This committee debates and amends legislation but cannot pass a bill. Rather, all bills considered by the Committee of the Whole or listed on the House Calendar must undergo debate and passage by the full House. A simple majority is required for passage.

Passage of the bill to the Senate

Upon approval by either the House of Representatives or Senate, the bill moves on to the other for consideration. Thus, a House resolution is passed to the Senate and vice versa. However, if the bill is of a non-controversial nature, the Majority Leader may ask for unanimous consent for immediate consideration and order a vote with little or no debate.

One of the key differences in the Senate proceedings is that there is no fundamental 'germaneness rule.' Whereas in the House, any proposed amendment must be germane to the underlying bill (relevant or affects the underlying bill), Senators may try to introduce legislation by tagging their amendment onto unrelated bills being debated on the Floor.

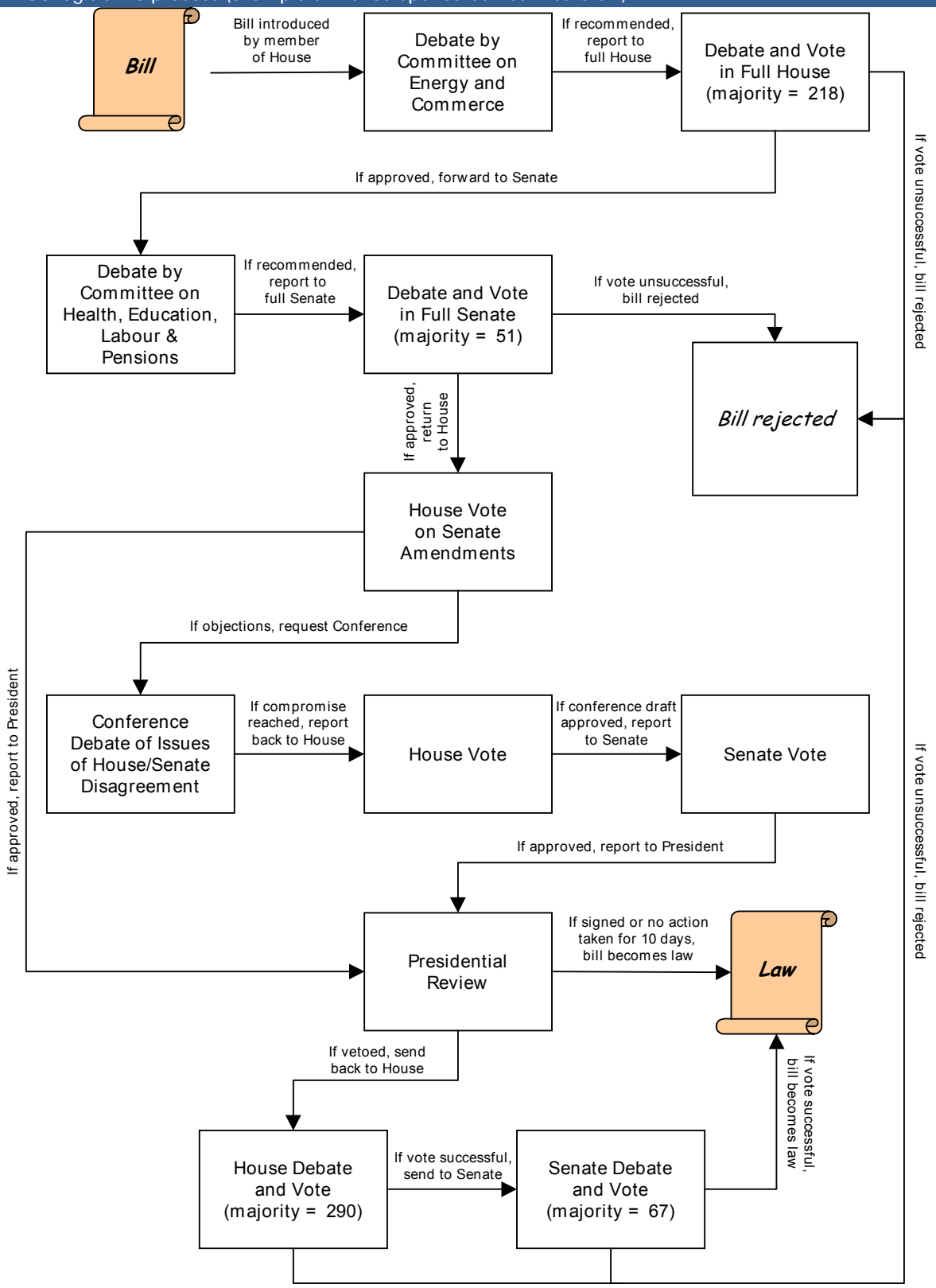
Resolution of disagreements

Following Senate approval, the bill, engrossed with new amendments, returns to the House. If there are no objections to Senate amendments, the bill is immediately presented to the President. In the event of disagreements, the originating house may request a conference. During the conference, which includes members from each house (generally members of the relevant committees), discussion is strictly limited to matters in disagreement. If a compromise is reached, the bill must again be voted on and approved by both houses. Only after a bill has been passed in identical form by the House and Senate may it be presented to the President.

Presidential approval or veto

Once approved by the legislature, the bill is given to the President. The President has three options: 1) he may sign it into law, 2) he may do nothing, whereby after ten days (excluding Sundays), the bill automatically becomes law, or 3) he may veto it. If the bill is passed via either of the first two options, it becomes law immediately, unless the bill expressly specifies a different date. In the event of a veto, Congress may override the President's decision if both houses achieve a two-thirds majority in favour of the bill. However, if the vote is unsuccessful, the bill is rejected.

Figure 92: US legislative process (example of House-sponsored healthcare bill)



Source: Deutsche Bank

Legislative dictionary

Act - Legislation that has passed both chambers of Congress in identical form and signed into law. Sometimes also refers to a bill which has been passed by one house.

Amendment in the nature of a substitute - An amendment that strikes out the entire text of a bill and inserts a different full text.

Bill - Draft legislation introduced by either the House or the Senate, not yet enacted into law. Designated H.R. and S.R. followed by a number, for House and the Senate bills, respectively. Similar in function to a joint resolution.

Calendar of Business - One of the two calendars of the Senate, covering all public and private bills and resolutions.

"Clean Bill" - A new bill (with a new number) that encompasses in a clean draft the text of a previous bill, including all amendments. Designed to expedite legislative action by avoiding separate floor consideration of each amendment.

Cloture - A Senate motion to limit the length of debate on a particular bill, in order to prevent filibustering. Requires three-fifths vote for passage.

Committee of the Whole – Essentially, the full House operating under a different set of rules that requires only 100 members (instead of 218) for a quorum. Permitted to debate and amend, but not pass legislation.

Committee on Rules - Reports special rules that set the terms for debate and amendments on specific measures.

"Companion Bill" - A bill or resolution introduced by one house that is similar or identical to legislation introduced by the other. Intended to promote simultaneous consideration of a measure.

Concurrent resolution - A measure used to deal with matters affecting both houses of Congress. Designated H. Con. Res. or S. Con. Res. for House and Senate resolutions, respectively. Does not require presidential approval.

Conference - A temporary panel of House and Senate representatives convened to resolve disagreements on a bill that has passed through both chambers.

Corrections Calendar - One of the calendars of the House, containing resolutions eligible for expedited passage. Matters are generally specific, non-controversial issues or narrowly targeted bills. Passage from this calendar requires a three-fifths majority.

Discharge Calendar - The calendar of motions to discharge committees from consideration of certain public bills or resolutions.

Engrossed Bill - The official copy of a bill or resolution passed by the House or Senate.

Enrolled Bill - The final copy of a bill or resolution passed by both chambers in identical form. Printed on parchment paper, signed by House and Senate officials, and submitted to the President for signature.

Executive Calendar - One of the two calendars of the Senate, covering treaties and nominations.

Filibustering - Excessive Senate debate and/or procedural motions intended to block or delay action on a particular bill.

Germaneness rule - A rule in the House preventing the proposal of irrelevant amendments. No such requirement exists in the Senate, allowing for the addition of unrelated amendments, often called "riders".

House Calendar - The second of the two primary legislative slates of the House. Includes all public bills that do not raise revenue or appropriate money or property.

Joint resolution - Draft legislation introduced by either the House or the Senate, not yet enacted into law. Designated H.J. Res. and S.J. Res. followed by a number, for House and the Senate resolutions, respectively.

Majority/Minority Whips - Act as Senate floor leaders in the absence of Majority/Minority Leaders. Often responsible for rallying party votes on major issues.

Motion to discharge committee - A motion to discharge a committee from the consideration of a public bill or resolution that was referred to the committee 30 days prior thereto. Requires a majority vote for passage.

Motion to recommit/reconsider - A motion to reconsider a question already decided by vote. Rules generally permit one motion to reconsider any issue. Usually offered by a supporter of the outcome immediately after the vote, followed by another motion by the same Senator (or other supporter) to table the motion, thus securing the outcome of the vote.

Motion to suspend the rules - A motion to bypass usual procedure and bring a matter before the House for immediate consideration and passage. Generally proposed for routine legislation perceived to have a broad degree of support.

"Pocket Veto" - A veto that occurs indirectly, because Congress has adjourned before the end of the President's ten-day window to take action on a bill.

Point of order - A claim that a rule of the House or Senate has been violated.

President of the Senate - Presiding officer of the Senate, officially, the Vice-President. They may (but are not required) to vote in the case of a tie. Duties performed by the President Pro Tempore (and others designated by him) during the Vice-President's frequent absences.

President Pro Tempore - Constitutionally appointed officer who presides over the Senate in the absence of the Vice-President. By custom, the Senator of the majority party with the longest record of continuous service.

Private Calendar - A legislative slate of the House that includes all bills and resolutions relating to a private matter.

Quorum - The number of members required to do business – generally, a simple majority (218 in the House, 51 in the Senate).

Senate Majority/Minority Leaders - Elected by their respective parties to serve as chief Senate spokespeople and to manage and schedule the legislative and executive business of the Senate.

Simple resolution - A measure used deal with matters affecting only one house of Congress. Designated or H. Res. or S. Res. for House and Senate resolutions, respectively. Does not require presidential approval.

Speaker of the House - Member of the majority party who serves as presiding officer of the House. Traditionally refrains from debating or voting and does not sit on any standing committees. Second in line to succeed the President.

Time agreements - A motion in the Senate to limit the time for debate, specify speakers and/or control the addition of amendments. Requires unanimous consent for approval.

Union Calendar -The first of the two primary legislative slates of the House. Includes all public bills appropriating money or property or authorising an undertaking by a governmental agency that will incur an expense to the government.

Veto - Rejection of a bill or resolution by the President. Usually returned to the originating house, stating objections. May be overridden by a two-thirds majority vote of both the House and Senate.

Pharmaceutical marketing

Introduction

The importance of marketing in the success of a new or existing drug cannot be underestimated. With increasing costs associated with drug development, and decreasing time between the launch of innovative products and fast-following, 'me-too' versions, there has been a greater focus on maximising revenue from newly approved drugs before competitors enter the market. Consequently, the major drug companies have recognised that a strong marketing message and rapid penetration of the potential market are both vital if a drug is to attain peak sales as rapidly as possible and maximise the total revenue achievable over its patented life.

This recognition has seen several important developments. Drug companies have spent more on clinical trials post-launch in order to differentiate their product and strengthen the marketing message. Greater emphasis has also been placed on influencing key opinion leaders such as hospital specialists, ahead of a product's launch. Beyond this, the advent of direct-to-consumer (DTC) advertising in the US has seen drug companies invest heavily in consumer-orientated television and press advertising, as they have sought to influence the ultimate consumer of the drug, i.e. the patient, to direct physician prescribing. Increasingly, the industry is also moving towards global launches, meaning launches across different geographic territories occur within a much narrower timeframe than was the case historically. This has been helped by the gradual harmonisation of the regulatory process in the markets of Europe, the US and Japan.

Sales and marketing focus

Targeting decision makers

Pharmaceutical markets are different from many other markets in that the choice of drug is made by a third party (physician), rather than the end consumer or payor. Hence, the bulk of the drug company's sales and marketing effort has traditionally focused on general practitioners, consultants and hospital specialists who determine which medicine a patient should take, rather than payors such as the government, managed care organisations or health insurers. However, relationships with these groups have assumed greater importance, as they make the critical decision of determining the drug's inclusion in the formulary (for reimbursement), as well as its relative position within the formulary. Not being in the formulary means not being able to receive reimbursements, which in turn discourages prescriptions. As a higher proportion of managed care migrates to a multi-tier system of co-payment, obtaining a favourable position as a "preferred brand" may be critical in ensuring uptake of the drug among physicians and patients. Therefore, health economics has taken on a more prominent role in pricing and formulary negotiations with the relevant authority, i.e. it may be cheaper to reimburse the cost of the new drug than to have to pay later for hospitalisation costs or time lost at work due to illness.

Distribution

The pharmaceutical company's approach to marketing will also differ depending on whether the drug is to be used in a hospital or prescribed through a physician's practice (sold through retail pharmacies). Niche products targeting hospital specialists, as a rule, require a considerably smaller sales force. In addition, drugs used in the hospital environment may achieve more modest prescription volume than those aimed at the

mass retail market. However, this does not necessarily mean that revenues will be small; for example, biological products such as α-tumour necrosis factor inhibitors and targeted cancer therapies are able to charge high prices because of their efficacy despite a small target segment, and have achieved billions of dollars of sales annually.

Drug lifecycles

The lifecycle of a drug can be broken down into five phases: pre-launch, launch/growth, extension, maturity and patent expiry.

Pre-launch

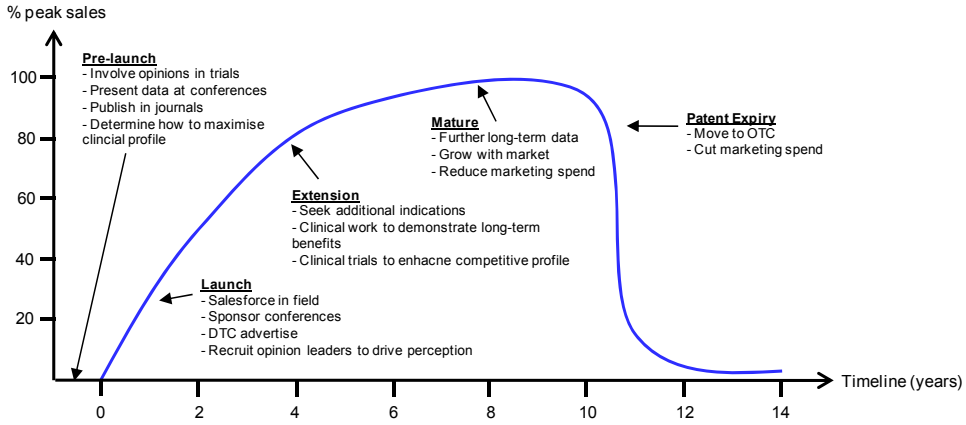
The pre-launch phase encompasses the work that is undertaken to prepare the market for the new drug while it is still going through the clinical trials and registration process. It can be broadly broken down into events that occur internally or externally.

- Internally, within the company, marketing and research departments work together to create a clinical data package. It will highlight results which portray the drug's best attributes, and position it as favourably as possible in the eyes of the medical fraternity and patients. The goal of the marketing department will be to create a clear and simple message – of what the drug is and why it should be used, and devise a marketing plan of how this message is to be effectively communicated to the target market.
- Externally, pre-launch initiatives involve influencing key opinion leaders in the relevant field and promoting the drug's benefits to the wider medical community. While the actual marketing of an unapproved entity is prohibited by regulators, much can be done to increase market awareness and ensure that those with influence have a positive opinion of the new drug ahead of launch. Efforts here include enlisting experts in the field to oversee clinical trials, presenting clinical data at conferences, publishing clinical findings in leading journals and, in general, creating as much awareness within the medical fraternity as possible of the potential benefits of the treatment in development.

Launch/growth

The growth phase involves the all-important launch of the drug for its lead indication. Having already prepared the market previously, the company will now focus on increasing patient and physician awareness. Here, the scale and effectiveness of the sales force are key factors; and contract sales representatives may be used to enhance the efforts of the company's own sales representatives during this critical period. Out in the field, the sales force will seek to inform as many physicians as possible of the drug's approval, providing them with free samples for patient use (sampling) and extolling the new drug's virtues. Managed care organizations will also be targeted as the pharmaceutical company attempts to get the new drug included on formularies. The company will sponsor conferences and seminars where key opinion leaders will speak about the benefits of the new drug, as it seeks to disseminate information and increase awareness. Pharmacists will also be contacted and made aware of the drug's release. Some months into the launch, direct-to-consumer advertising may also be employed to drive consumer awareness.

Figure 93: Lifecycle of a drug



Source: Deutsche Bank

Extensions

The extension phase in the lifecycle of a new drug broadly involves obtaining new treatment indications and enhancing the competitive profile of the drug.

- **Line extensions/additional indications**. Most drugs can be used for more than one disease. For example, schizophrenia drugs also find use in bipolar disorder, while cancer drugs may be used for more than one type of cancer. This increases the potential patient population who may benefit from the drug. Usage in these expanded indications are covered by their own exclusivity, hence helping to extend the marketing exclusivity period of the drug. The effect is to broaden the drug's total market opportunity.
- **Competitive profile**: Throughout the life of the drug, most companies will also look to sharpen the drug's clinical data package and competitive profile. Further clinical trials will be undertaken with a view to show the long-term benefits of treatment or to demonstrate that it is more efficacious than other competitors in the same class. Following approval from the regulatory bodies, data collected from these trials can then be included on the drug's label and used in promotional messages.

Maturity

Efforts to extend a drug's range of indications and its competitive profile may continue for much of the drug's life. However, through its later years of patent protection, growth will largely reflect that of the underlying market. As the drug finally approaches the end of its patent life, investments and marketing spend will start to tail off given the lack of further opportunity to recoup any expenditure on marketing. The strategy is essentially to treat the drug as a cash cow.

Patent expiry

Following patent expiry, revenue may fall sharply, depending on whether generics enter the market, and whether marketing support is withdrawn. Depending on the nature of the product, the drug company may seek to gain approval to sell the drug over the counter (OTC), i.e., as a branded non-prescription medicine (e.g. GlaxoSmithKline's Alli, Sanofi's Allegra). In addition, several firms have recently introduced their own 'authorised' generic products following patent expiry in order to retain a modest fraction of their former revenues (e.g. Shire's Adderall XR).

Sales force size

In assessing a company's sales force, sheer numbers is only one aspect of the issue. The marketing resource that is committed to support a particular drug is also critical. In other words, a sales force of 5,000 promoting 30 products may be of less value than 3,000 promoting one drug. Consequently, pharmaceutical companies will make the decision to devote a substantial proportion of their sales effort towards supporting a drug's initial launch, especially if they have determined that it has the potential to become a blockbuster.

There is, of course, another benefit to sales force size and geographic presence. The stronger a company's sales representation, the more attractive it is as a co-marketer of choice for new products emerging from smaller companies' pipelines. This point has been well demonstrated by the historical success of Pfizer's co-marketing arrangements with Eisai for Aricept and Bristol-Myers Squibb's partnership with Sanofi to market Plavix.

The past ten years have seen a major shift in companies' attitudes towards the role of sales representatives in the all-important US market. In the early to mid-1990s, the growth in importance of the managed care organizations as providers of health coverage led to the view that these organizations would increasingly dictate which drugs would be prescribed by physicians. As such, the industry believed that less time was needed to be spent on detailing physicians and more on the less labour-intensive and larger managed care groups. The result was a reduction in sales force sizes. However, although managed care organizations established drug formularies (albeit not very restrictive), the physician remained the predominant decision-maker. Consequently, there has therefore been shift back towards a focus on marketing to the physician base.

From the early 2000's until the last few years, pharmaceutical companies have engaged in a war of numbers as companies competed in marketing spend in order to capture market share in their key products. In recent years, however, the loss of patent protection for key blockbuster drugs has hurt sales, as generic copies entered the market at a fraction of price of branded drugs. In addition, a dearth of new drug approvals from barren pipelines has left the sales force with few new drugs to sell. Hence, the pendulum has swung back, as pharmaceutical companies embark on large cuts in the size of their sales force in an attempt to cut costs and shore up earnings during this difficult period.

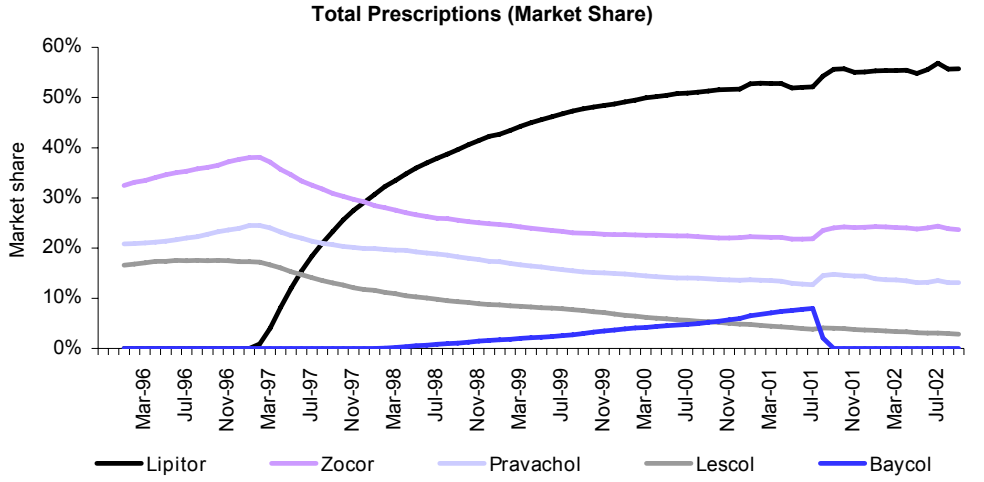
Drug profiles

As therapeutic markets have become more competitive and marketing more important, so drug manufacturers have invested more in trying to differentiate their products and provide their sales force with a clear marketing message. For any drug, high efficacy, a favourable side-effect profile and a convenient dosing schedule that favours compliance (e.g. oral, once a day) is more likely to facilitate penetration among physicians and patients. However, to the extent that the drug company can build on these claims by undertaking further clinical work to broaden a drug's range of indications or demonstrate superiority vis-à-vis other class competitors, the marketing message can be enhanced. New claims can also serve to re-invigorate the drug sales force, providing them with a new message to market to physicians.

The importance of a drug's profile and the impact it can have on performance are well illustrated by the phenomenal success of Pfizer's cholesterol-lowering drug, Lipitor.

Despite being the fifth drug of its type to market, Lipitor's superior profile combined with Pfizer's marketing and sales force resulted in one of the most spectacular launches in the industry's history. By contrast, the result of getting the profile wrong, by misreading the market and not putting sufficient sales resources behind a drug was illustrated by Bayer's early experience in the same market with its cholesterol lowering drug, Baycol (which was subsequently withdrawn following deaths associated with a later introduction of a higher dose). Despite being priced at only 80% of Lipitor's level, prescriptions for Baycol were disappointing, as the company mistakenly considered that price rather than efficacy would drive market share (see Figure 94).

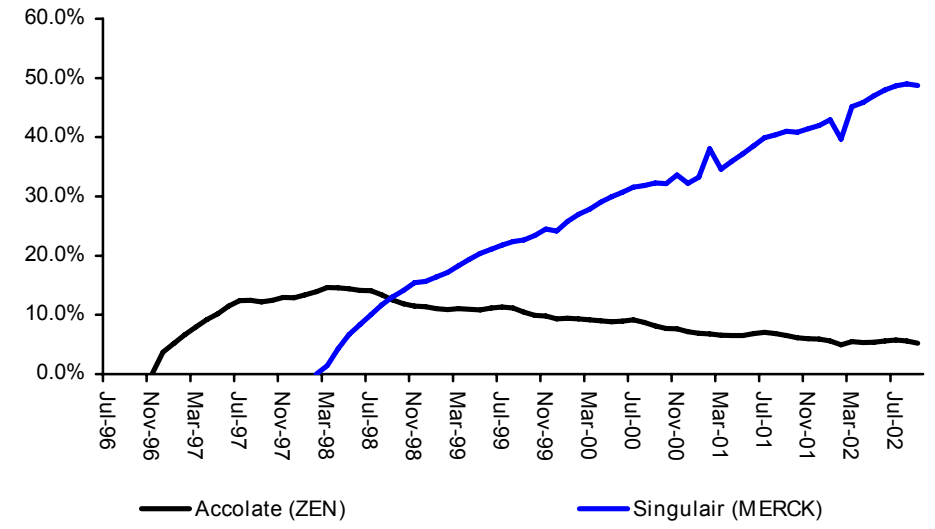
Figure 94: Cholesterol-lowering US market shares 1996-2002



Source: IMS Health

Similarly, the performance of AstraZeneca's Accolate against that of Merck's Singulair demonstrates how marketing savvy can lead to excellent results. While both products have similar profiles, Merck delivered a clearer and more distinct marketing message despite being second to market, which helped Singulair grow its sales at the expense of Accolate. The profiles also demonstrate physicians' clear preference for a once-a-day formulation – Singulair is taken once a day against twice a day for Accolate (Figure 95).

Figure 95: Leukotriene antagonist US market shares (1996-2002)

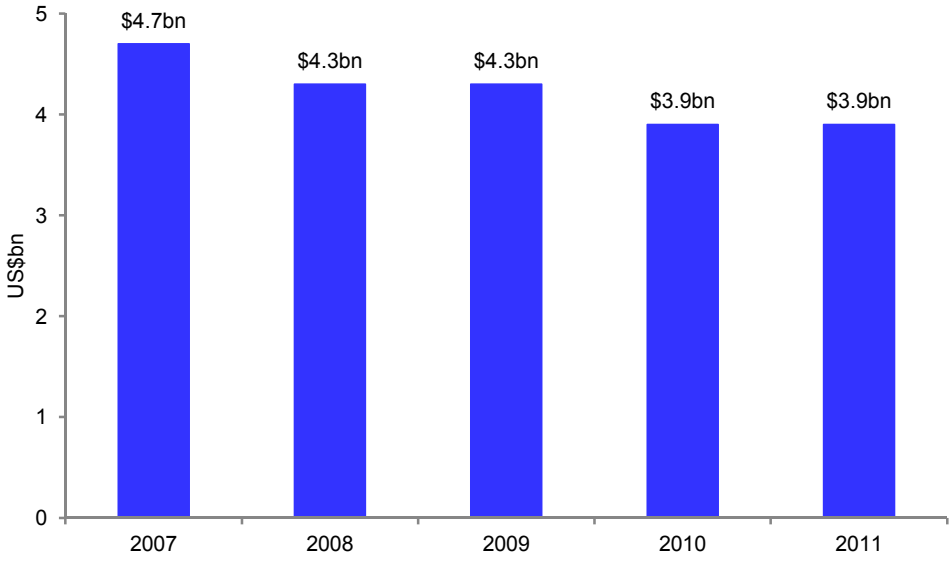


Source: IMS Health

Direct-to-consumer advertising

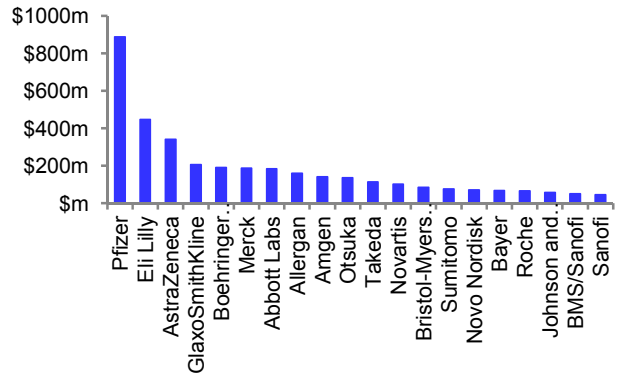
The liberalisation of restrictions on broadcast advertising of drugs in the US by the FDA in 1999 saw television and radio advertisements emerge as mediums in which pharmaceutical companies were able to promote their products. This saw the rise of Direct-to-Consumer (DTC) advertising, where companies targeted consumers directly in order to increase brand and disease awareness. DTC spending rose from c.$150 million in 1993 to $4.7 billion in 2007. The global economic downturn and loss of patent expiry for key drugs put pressure on marketing budgets over 2007-11.

Figure 96: DTC spending 2007-11 ($m)



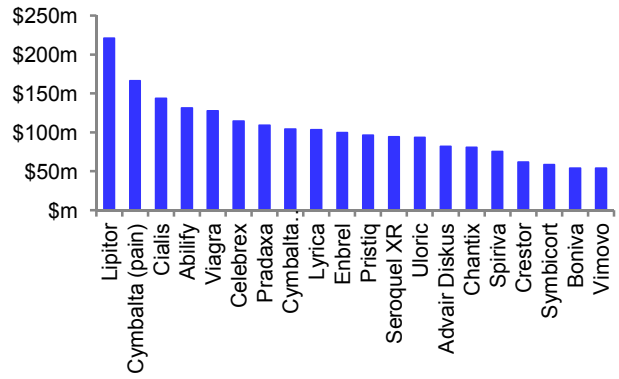
Source: Nielsen

Figure 97: Top companies by DTC spend, 2011



Source: Nielsen

Figure 98: Top 20 brands by DTC spend, 2011



Source: Nielsen

DTC advertising places advertisements for prescription drugs in magazines, on television, on radio and, more recently, on the Internet. It has been legalised in the US, but not in Europe or Japan. DTC advertising has focused particularly on drugs used to treat so-called life-style disorders (e.g.,diet, impotence or hair loss), and drugs for diseases where the consumer may influence the physician's decision (e.g., high cholesterol).

However, we note that advertising occasionally works as a double-edge sword, with companies being sued for alleged false or misleading advertisements. Lawyers have also turned to DTC advertising, and we have observed a worrying trend of increased DTC advertising by tort lawyers offering their services in lawsuits against drug companies, on behalf of patients that have suffered side-effects from certain drugs.

Assessing new drug launches

Expanded sales forces and the advent of direct-to-consumer marketing have recently led to the take-off of new drugs following launch. As a result, the success of a new drug is being judged by analysts much earlier than before, especially with the availability of prescription scrip data available on a weekly basis. However, the launch profile of a drug is still likely to vary considerably, depending on the disease which is targeted.

In a disease for which physician visits are common and where patients are generally given short courses of treatment, we would expect a successful drug to enjoy a rapid take-off, particularly if a new product is believed to be more effective than existing therapy. Products in this category would include antibiotics.

In contrast, a drug targeted at a disease for which the majority of patients receive long-term therapy would generally experience a slower launch than a drug for acute treatment. This is because a significant proportion of patients who are stable on a particular therapy are adverse to changing treatments, unless there is poor control of symptoms or problems with side-effect. As a result, the take-off of new drugs in this category tends to be slower, driven predominantly by the diagnosis of new patients.

The launch trajectory of drugs used in chronic therapy also depends on the size of the potential patient population. Drugs treating common conditions, such as hypertension,

can enjoy strong launches in terms of volume, even though the majority of existing patients are on repeat prescriptions.

Drugs for diseases that have previously not been routinely treated by primary care practitioners are also likely to experience a slow launch. In these cases, the pharmaceutical company needs to build the market from scratch by educating physicians and by targeting patients through direct-to-consumer advertising. An example for this is irritable bowel syndrome, where the majority of patients self-medicate. The speed of take-off for a drug in a new disease depends of the frequency and severity of symptoms experienced by patients and their level of motivation in going to the doctor. Certain diseases for which there is a high level of patient motivation, such as obesity and smoking cessation, have in the past seen strong launches.

Finally, new drugs with genuine life-saving potential in a disease where existing therapy is ineffective, such as breakthroughs in cancer treatment, tend to achieve a high level of patient penetration relatively quickly. However, the majority of cancer drugs see their sales increase incrementally as approved indications expand from second or even third-line use in a specific tumour type to first-line use in a broader range of cancers.

Emerging markets

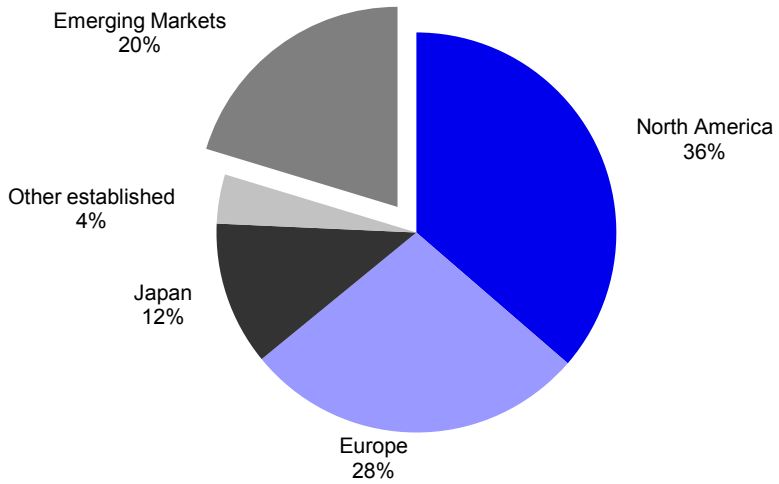
- Emerging markets offer accelerated sales growth, but at lower profitability.
- Local players benefit disproportionately from growth as EM governments target development of local expertise.
- Leading companies include Sanofi, Pfizer, Novartis and Bayer.

Emerging markets (EM) represent countries which are in transition between developing and developed status. This category now comprises some 50 or so countries, depending on which classification is followed, though the commercial opportunity is seen as concentrated in a subsection of this group.

Introduction

Pharmaceutical sales in Emerging Markets (EMs) reached $194 billion (+12%) in 2011, according to IMS Health, equivalent to 20% of the global total (Figure 99). Within EMs, some 45% of sales were generated in the so-called BRIC group of countries (Brazil, Russia, India, China) with the remaining 55% accounted for largely by around 50 small- to mid-sized countries. These same markets account for around 85% of the world population, the massive mismatch between sales value and population indicating the theoretically huge upside for the pharma industry from EMs.

Figure 99: Global pharma market by sales (2011: $955bn, +5%)



Source: IMS Health data)

Profitability in this diverse set of developing markets is inevitably below that of the West as a result of lower pricing. Nevertheless, the huge volume growth opportunity - driven by improved healthcare infrastructure, a rising and increasingly affluent middle class and greater longevity (hence the increasing prevalence of chronic diseases such as hypertension and diabetes) - has been seen as an important prop for the pharma industry during its 'patent cliff' as well as a key source of long-term growth.

EMs have in recent years represented an easy win for the pharmaceutical industry with modest investment generating solid returns from 'tail' (mature or patent expired) portfolios. Through 2005-10 the industry benefited from double-digit volume growth as rising wealth pulled a greater number of people into the middle classes on a global basis. With generally limited official reimbursement, systems have evolved with the non-medically educated populace bearing the bulk of the treatment cost. This was a bonanza for companies selling low-innovation branded medicines that offer minimal incremental benefit over true generics. However, with no financial stake in the innovative pharmaceutical industry at present and an overarching requirement to improve healthcare provision, EM governments have the opportunity to build healthcare systems that benefit their own populace and companies (jobs).

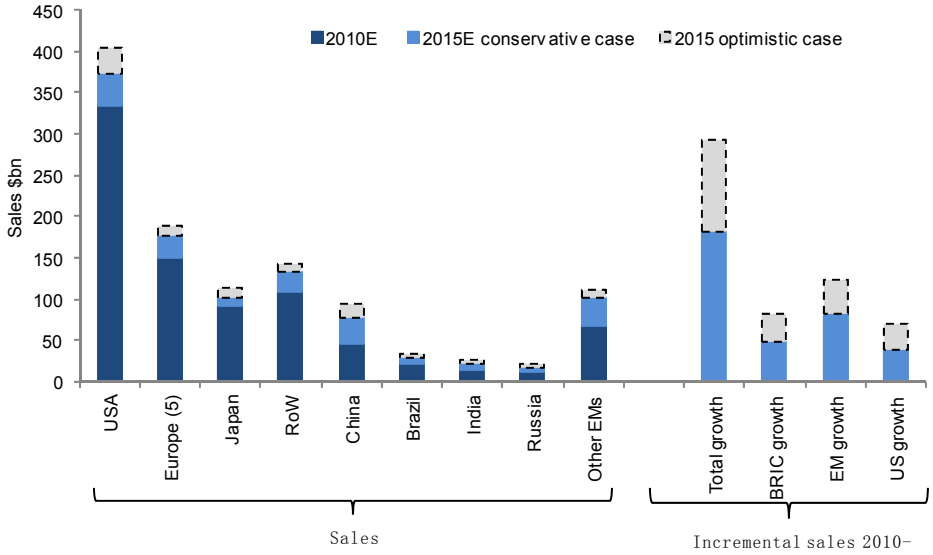
Figure 100: Headline statistics

	Drug exp ($bn)	2011-2015 CAGR	% Total market	Population (m)	GDP per capita ($)	Total HC exp per capita	Total HC exp as % GDP
North America	344.4	1-4%	36%	335	48,639.0	7,601.66	16%
EU5	159.1	(-1)-2%	17%	314	39,321.2	3974.214	10%
Japan	111.2	1-4%	12%	127	45,902.7	3754	8%
China	66.7	15-18%	7%	1,349	5,429.6	191	5%
Brazil	29.9	12-15%	3%	195	12,593.9	734	6%
Russia	15.7	10-13%	2%	143	13,089.3	476	4%
India	14.3	14-17%	1%	1,225	1,488.5	44	3%
Rest of World	214	2-6%	22%	3,207	14,945.0	440	3%
Total	**955.4**	**3-6%**	**100%**	**6,894**	**10,033.6**	**900**	**9%**

Source: World Bank 2010, IMS Health, 201h, Deutsche Bank

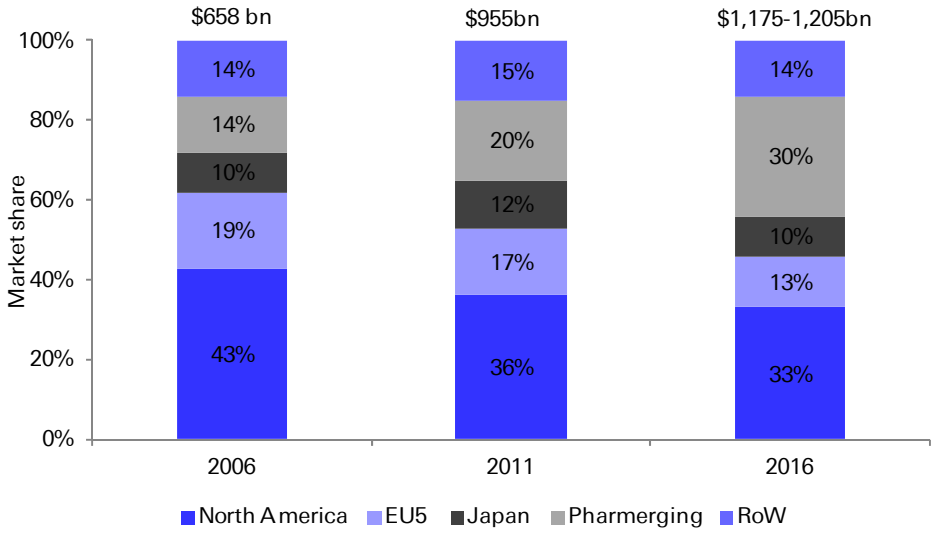
We discuss emerging markets as a single concept but in reality they are a diverse group of pharmaceutical markets at different stages of development following vastly different futures. The so called BRIC countries (Brazil, Russia, India and especially China) do merit detailed individual discussion, however. Pharmaceutical and OTC sales in BRIC reached a total of c.$127 billion in 2011 – equivalent to around half the size of the top 5 European markets and Japan combined. Based on our predicted growth rates, emerging markets in aggregate will provide incremental sales of c.$90-150 billion (half of global sales growth) from 2010-15E accounting for c.25% of global sales by 2015E (compared to c.20% in 2011). Over half of the growth in EMs will likely come from BRIC, we estimate. Figure 102 shows that EMs will be increasingly important to global pharmaceutical sales.

Figure 101: EMs dominate Pharma growth (offsetting patent expiries elsewhere)



Source: Deutsche Bank forecast. IMS health.

Figure 102: EM to account for increasing proportion of global sales



Source: Deutsche Bank, IMS Market Prognosis, Apr 2011

Figure 103: Top 20 pharma markets by sales, 2011 and 2016E (EMs shaded)

Rank	2011	Sales index	2016	Sales index	*Change in rank*
1	United States	100	United States	100	
2	Japan	36	China	39	*+1*
3	China	21	Japan	36	*-1*
4	Germany	14	Brazil	15	*+2*
5	France	12	Germany	13	*-1*
6	Brazil	9	France	11	*-1*
7	Italy	9	Italy	8	
8	Spain	7	India	7	*+5*
9	Canada	7	Russia	7	*+2*
10	UK	7	Canada	6	*-1*
11	Russia	5	UK	6	*-1*
12	Australia	4	Spain	5	*-4*
13	India	4	Australia	4	*-1*
14	South Korea	4	Argentina	4	
15	Mexico	3	South Korea	4	*-1*
16	Turkey	3	Mexico	3	*-1*
17	Poland	2	Venezuela	3	*+1*
18	Venezuela	2	Turkey	3	*-2*
19	Netherlands	2	Indonesia	2	
20	Belgium	2	Poland	2	*-3*

Source: Deutsche Bank
Index in each year based on ratio of country spending to U.S. spending (in constant $) in the year

Emerging markets have many characteristics which make them attractive for pharmaceutical companies. They are generally fast-growing economies with relatively high GDP growth, giving them an increasingly significant share of the global economy. They also represent the vast majority of the world's population, and their population numbers are expected by economists to grow at a faster rate compared to developed economies. Governments with growing fiscal budgets have focused on increasing basic healthcare coverage for their citizens. Lifestyle and dietary changes among the population as a result of their newfound prosperity has seen a rise in diseases such as diabetes and hyperlipidaemia. A growing economy has also given rise to a middle class who are increasingly discerning and willing to pay out of pocket for drugs.

Expansion in emerging markets is though associated with inherent risks. Respect for and enforcement of intellectual property rights surrounding drugs is still lacking (in some markets) compared to developed countries. Government regulation and policy are less stable and may change with little notice, forcing companies to react quickly to unexpected developments. Sparse infrastructure, undeveloped distribution networks and a lack of trained local staff may also require large upfront investments.

Market share

Current sales in emerging markets reflect the focus which management has, consciously or unconsciously, historically placed on these countries. Given the economic growth of these countries in recent years, we now see a divide between pharmaceutical companies which have had a long history and hence strong presence, and companies which have been late to the game. In the latter's attempts to catch up, we are concerned that the 'land grab' strategy may potentially dilute earnings or have a negative impact on shareholder value, as companies overpay for local acquisitions.

The larger European pharma companies are generally well represented in the EMs, generating some 24% of sales from the region, representing roughly double the average exposure of US large-cap peers (Figure 104 and Figure 105). Individual company exposures inevitably vary, from AstraZeneca at the low end (17%) to Bayer (33%) and Sanofi (30%) at the high end, reflecting a combination of company history (including colonial pasts and the degree of focus on M&A in EMs), and the nature of product portfolios.

Figure 104: EU large-cap Pharma summary exposure to EMs (% sales, EBIT)

	EM as % Pharma*	EM as % Group	EM margin (est**)	EM as % group (core) EBIT
AstraZeneca	17%	17%	35%	15%
Bayer	33%	36%	14%	37%
GSK	21%	25%	31%	25%
Novartis	23%	24%	28%	25%
Novo Nordisk	22%	22%	25%	16%
Roche	26%	27%	37%	28%
Sanofi	30%	30%	40%	33%
Mean (ex-Bayer/Novo)	**24%**	**25%**	**34%**	**25%**

*Note: * 2011 FY figures except GSK and Novartis (1H12) due to reporting format change; Pharma defined as branded and generic drugs plus vaccines (in case of Sanofi other businesses [CH, AH] included): Roche figures for International region; Novo for China plus International; GSK for EMAP; others for Emerging markets or Emerging growth markets;** pre-R&D margin; Bayer EM margin below peers due to MaterialScience and CropScience (Pharma EM margin assumed at 35%)*
Source: Company data, Deutsche Bank

Figure 105: US large-cap pharma exposure to EMs

	EM as % Pharma*	EM as % Group	EM margin (est***)	EM as % group (core) EBIT
Bristol Myers Squibb	4%	4%	25%	3%
Eli Lilly	10%	11%**	20%	8%
Merck	18%	19%**	28%	16%
Pfizer	16%	19%		
Unweighted US mean	**12%**	**13%**	**24%**	**9%**

*Notes: * based on FY 2011 results; ** DB estimates; *** EM margins are strictly DB estimates, which assume that margins are attractive, but below the corporate average; We are currently restricted on PFE and cannot provide any numbers that represent estimates*
Source: Deutsche Bank

Profitability well below developed markets

While the prospect of augmented sales growth is welcome in any industry, we are mindful that the key value of a market to any company is in its incremental profits generated. In this instance, we note that profitability in this heterogeneous collection of markets is much lower than in Western markets. IMS data shows that on average, prices are c.50% lower in emerging markets, which is only partly offset by lower costs. As a consequence, we estimate the profitability of the European companies' EM businesses is typically 20-50% below that in the developed markets on a pre-R&D basis (where reported, companies generally do not apportion R&D spend to EMs, although we think this is increasingly questionable given our view on the long-term outlook for EMs). As shown in Figure 106, Sanofi generates a pre-R&D margin in EMs of around 40% while GSK - with less critical mass - achieved a circa 31% margin in 1H12. The latter compares with a >60% pre-R&D margin in GSK's developed markets.

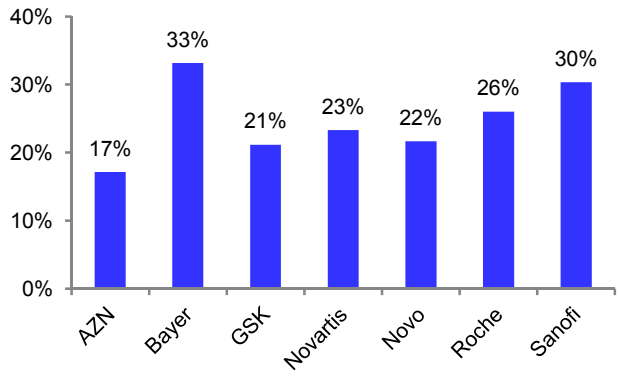
Figure 106: Profitability in EMs (where disclosed)

Company	EM profitability	Source
AstraZeneca	Pre-R&D operating margin (excluding central costs) was 73% of that in established markets in 2011	Company general IR presentation, May 2012
GSK	1H12 pre-R&D margin in EMAP region was 30.9% (as compared with 62% in established markets)	1H12 results press release
Sanofi	EM business operating margin forecast at "around 40%" excluding central administrative and R&D costs in 2011 (vs estimated pre-R&D margin for established markets of 49-50%)	IR "Strategy & Outlook" thematic seminar, Sep 2011

Source: Deutsche Bank, company data

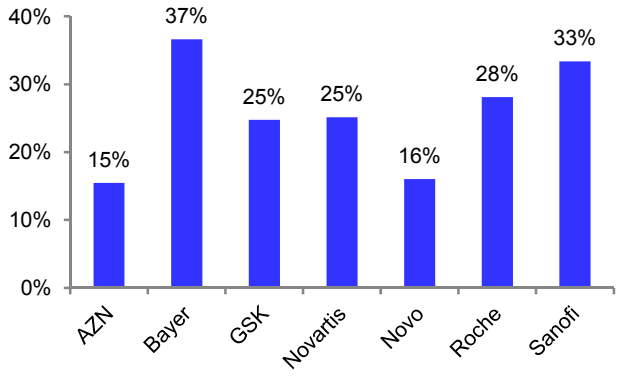
Excluding an allocation for R&D means that EMs nominally generate a similar proportion of group EBIT to their sales contribution, by our estimates (the likely exception, we believe, is Novo Nordisk which has a heavy exposure to low-priced insulin tender business in the EMs). This is shown graphically in Figure 107 and Figure 108.

Figure 107: EMs as % Pharma/vaccines sales (2011*)



*Note: * 1H12 for GSK and Novartis due to re-classification of EM sales*
Source: Deutsche Bank

Figure 108: EMs as % group (core) EBIT (2011E*)

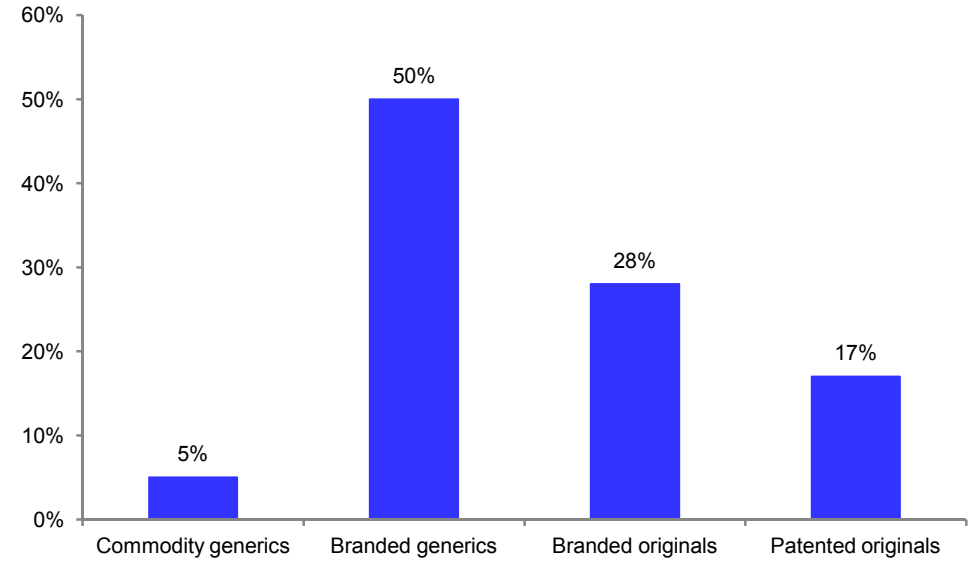


*Note: * 1H12 for GSK and Novartis due to re-classification of EM sales*
Source: Deutsche Bank

Branded generics dominate sales

In developed countries, once a drug loses patent protection, sales fall almost immediately as a result of generic competition as physicians and patients are generally indifferent between branded and generic drugs. In emerging markets, possibly due to less stringent regulation of local generic manufacturers, there is a perception of branded drugs being of higher quality. This has led to the development of 'branded generics,' which are generic drugs produced by third-party manufacturers, but sold at a premium under the brand of the pharmaceutical company, and by the sales force of the company. These currently attract higher prices and profitability compared to local unbranded generics, and form a key part of the strategy of several companies playing 'catch-up' in these countries (Figure 109).

Figure 109: Breakdown of sales in EM markets



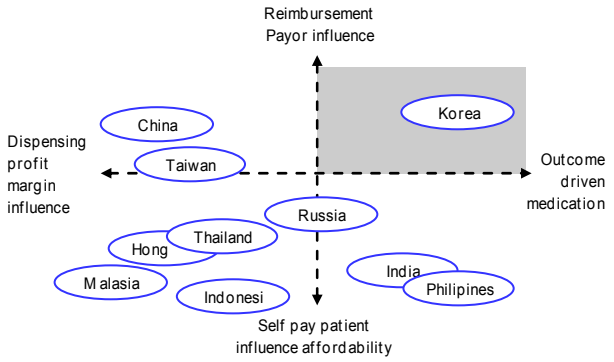
Source: IMS Health, AstraZeneca emerging markets presentation 2010

In the long run, however, we expect emerging markets to converge with the Western model. In the coming years, we expect healthcare expenditure as a proportion of GDP to increase, as these countries upgrade their healthcare systems and improve access for their people. Hence, optimistic market assumptions on emerging market growth apply current pricing and expect this to stay flat as volumes ramp. However, our in-depth analysis of worldwide pricing mechanisms suggests governments will not stand idly by and allow drug prices to contribute disproportionately to inflation:

- **Indirectly**, through policy designed to promote generics (tenders, positive lists, essential drugs lists and favourable pricing) we expect the **market to bifurcate** as the drug choice decision is taken away from the patient and physician and moves towards governments and pharmacists. This will result in markets more akin to Western markets with large low-cost generic sectors and small by volume but large by value innovative drug sectors. Notably, this should increasingly squeeze the cost-inefficient branded generics industry that currently dominates emerging markets. We expect this to be the primary target for price reductions in the future.
- **Directly**, we expect to see further price/reimbursement reductions to branded drugs across many markets, particularly in China and Russia, as an effort to control general inflation (notably there are no local political consequences from "bashing" Western pharma companies). In particular, we highlight the decision by Chinese authorities to cut the price of several drug classes (eg, cardiovascular drugs were subject to an average 19% price cut in 2011, including branded drugs available to the middle classes through the DRL system) while other drug classes are likely to suffer the same fate. We also highlight the Russian award of a tender to a largely unproven local Factor VII drug in place of the expensive brand from Novo Nordisk.

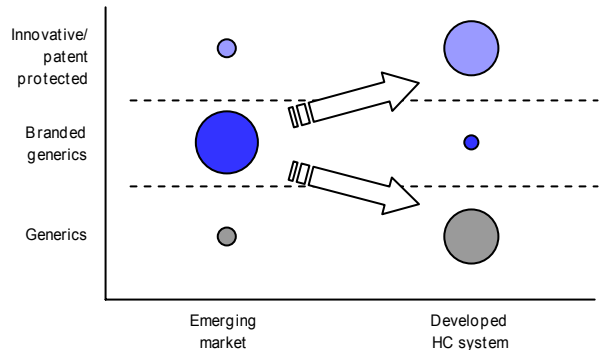
Ultimately, to manage these inherent risks to price, pharmaceutical companies need to offer constant innovation with patents that keep local generics and protectionist initiatives at bay (albeit, recognizing that IP is still sub-optimal in a number of markets).

Figure 110: Current positioning of HC systems



Source: Sanofi, Deutsche Bank

Figure 111: Over time innovation and generics win out



Source: Deutsche Bank

China

China embodies the excitement of emerging markets, representing the bulk of the future growth potential from this diverse group of developing nations. It already ranks as the number three market by pharmaceutical sales globally, behind the US and Japan, and is predicted by IMS to overtake Japan by 2016. Pure volume aspects from improved infrastructure investment and a rising standard of living make China extremely attractive for pharmaceuticals, but this comes at a cost of lower average pricing and profitability than Western markets. With virtually no national interests in innovative medicines and the ability to develop its pharmaceutical policy from scratch (or nearly) it is hard to envisage why a very savvy government would build a system in the pro-pharmaceutical manner of the US and Europe. As such, we expect long-term reform to continue the squeeze on pricing, particularly where Chinese alternatives exist and for a premium for true innovation for unmet need (not medicines in same class) to exist longer term. This makes investing in the near and long term two very different prospects, but for now companies can "make hay while the sun shines".

Pricing and reimbursement

The National Development and Reform Commission (NDRC) is responsible for setting and regulating the prices of various drugs in China. While drugs which are not reimbursed may be freely priced, international reference prices are still taken into consideration when drug manufacturers seek the NDRC's approval of their proposed price of these drugs. Drugs which are reimbursed by the government will usually belong to one of the following lists:

The **National Essential Drug List (EDL)**, which the Ministry of Health (MOH) first released in October 2009 as part of healthcare reforms, contains drugs deemed essential for the treatment of common medical conditions. Over 2012, the list of EDL drugs will be expanded from the initial 307 drugs (205 'Western' medicines and 102 traditional Chinese medicines) to c.800 drugs (consisting of c.500 'Western' medicines and c.300 traditional Chinese medicines). These drugs are subjected to price caps (set by the NDRC) to ensure fair pricing and accessibility of key medicines for the common citizen. These comprise mostly generic drugs and have to be purchased via tenders at the provincial level for public healthcare facilities. These drugs are included in the List A of the National Drug Reimbursement List, and are usually fully reimbursed under basic medical insurance (BMI) and the new cooperative medical scheme (NCMS) for rural regions (subject to annual limits on reimbursement). As the drugs on this list are usually

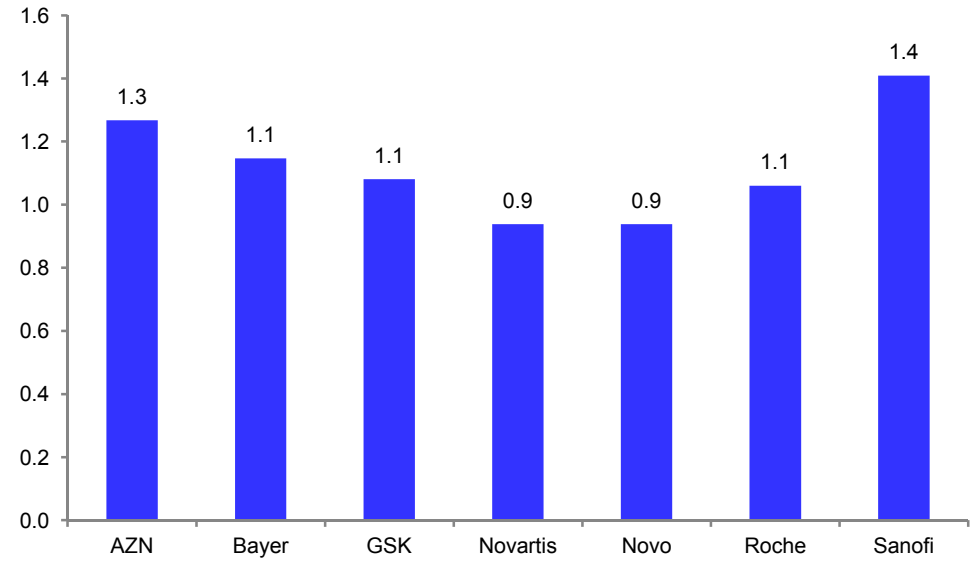
low priced and subject to regular price revision (downwards), the EDL is generally not a target for multinational pharmaceutical companies.

The **National Drug Reimbursement List (DRL)** contains drugs which are reimbursed under the BMI scheme, though the actual list varies between provinces. It is set by the MOHRSS at the national level, and is selected based on the advice of experts. The list had 450 drugs on List A and 1,400 drugs on List B in 2004, and was expanded in 2009 to include 503 drugs on List A and 1,624 drugs on List B. List A drugs, are usually generic low-cost products which are generally fully reimbursable. It includes all the drugs on the EDL and is the same in all provinces. The prices of its drugs are set by the NDRC. List B usually contains patented, more expensive drugs. Provincial governments have the flexibility to tailor this list to their own needs by adding or removing drugs, and need only include 85% of the drugs on List B in their provincial lists. Reimbursement (and levels of reimbursement) for List B drugs are determined by provincial governments and may vary from region to region. If drugs have been added to provincial lists, their prices will be determined by the respective provincial Development and Reform Commission (DRC), with input from the NDRC, and after which, the final price is set and filed with the NDRC. Access to the DRL B list is a target for multinational drug companies, although revision of the list is infrequent and inclusion on it can take a number of years post launch. Inclusion on the list can greatly enhance volume; however, this comes at a cost of profitability with fixed prices that are subject to revision (as evidenced, for example, by 19% average price cuts across a number of products in the hypertension and antimicrobial classes in 2011).

Generally, companies with mass market, branded original/generics/vaccines have higher proportions of their sales on the reimbursement lists whereas companies with innovative high priced medicines such as Roche have to generate additional sales from outside of this list (primarily to wealthy individuals).

Figure 112 shows the 2011 pharmaceutical sales of the leading European companies in China, indicating that Sanofi has the highest absolute exposure (it recently overhauled AstraZeneca to reach the #2 position by market share). Much the highest *relative* exposure though is enjoyed by Bayer which ranks #4 in the market (Figure 113) despite its modest global position in pharmaceuticals (#15). China consequently accounts for around 8% of Bayer's pharma sales versus 3-4% for its larger European competitors.

Figure 112: China sales of the EU pharma majors (2011, $bn; Pharma/vaccines)



Source: Deutsche Bank estimates

Figure 113: Leading player by share of Chinese pharma market, December 2011

Rank	Company	Change in rank since 2009
1	Pfizer	n/c
2	Sanofi	+2
3	AstraZeneca	-1
4	Bayer	-1
5	Ke Lun	+2
6	Roche	n/c
7	JS. Yangzijiang	-2
8	Shandong Qilu	n/c
9	JS.L.Y.G. Hengrui	n/c
10	Merck	(new top 10 entry)

Source: Sanofi (based on IMS Health data)

Looking ahead, although further price cuts and increased use of regional tendering are expected, IMS predicts that the Chinese pharma market will grow by c.18% in 2012, which looks achievable to us based on the 1H12 trends (the larger European pharma companies reported roughly 21% average sales growth in China in 1H12 in local currency terms while their US peers generally reported strong double-digit growth).

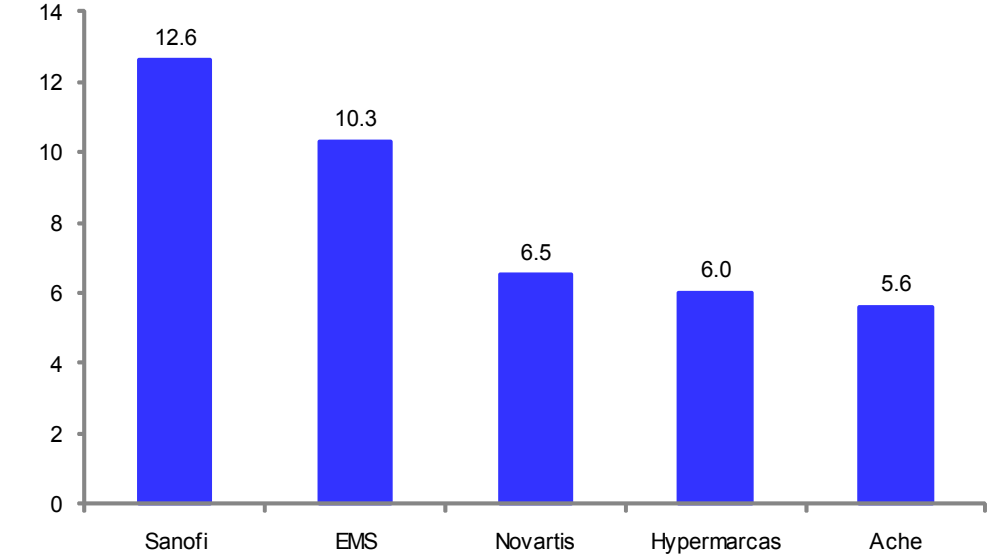
Longer term, we expect additional pricing pressure as more drugs are added to the EDL (up to an additional 500 drugs) and as the price premium of off-patent originator brands erodes. The latter may be accelerated by a move to remove the 15% hospital mark-up on drug prices (which historically generated up to half of hospital revenues and encouraged prescribing of higher-priced drugs) and by further evolution of government policies to address the growth in pharma spending. Against this physician and patient behaviour are unlikely to change quickly and the underlying volume dynamics remain strong, especially in the county and rural hospitals. The latter in our view will underscore double-digit medium-term market growth. In the very long term, however, the shifting climate will inevitably place more pressure on drug companies to innovate and to rely less on branded generics, making investing in the near and long term two very different prospects. However, for now companies can "make hay while the sun shines".

Brazil

We estimate that the LatAm pharma market was worth $67 billion in 2011, making it collectively larger than China ($56bn). Growth in the region has averaged 13% over the past six years and we predict growth will continue at around 10% pa in the coming years, led by Brazil (c.40% of regional sales, at c$26bn in 2011, according to IMS) but supported by Mexico, Chile, Colombia and Argentina.

The largely self-pay Brazilian market (which ranks 6th globally by pharmaceutical sales and is predicted to rise to 4th place by 2016, according to IMS) in particular offers a vibrant and attractive opportunity with an increasingly affluent population, a stable political environment, and good economic growth. We note that, compared with other emerging nations, Brazil already spends a high proportion of GDP on healthcare (>9%, vs EU countries at 10-12%, China at 5%), offering relatively high quality basic provision to the population. Hence, growth opportunities arise primarily through a direct translation of economic growth – notably through the increasing affluence of the fast-growing middle class - rather than through volume benefits from infrastructure improvements seen in so many other emerging markets. Pharmaceutical spend is currently predominantly out-of-pocket and the emergence of drug benefit insurers is likely to drive pharmaceutical sales growth above that of the wider healthcare market, creating opportunities for innovative drugs meeting high unmet needs as well as for cheaper generic medicines. Branded generic drugs are very popular in Brazil (as in many other self-pay emerging markets) and we note that Sanofi's market-leading position (Figure 114) was cemented via the $660m acquisition of the country's largest generics company, Medley, in 2009.

Figure 114: Leading pharma companies in Brazil by pharma market share (MAT Dec'11)



Source: Sanofi, IMS Health

Pricing and reimbursement

The Agência Nacional de Vigilância Sanitária (ANVISA) is responsible for the marketing approval of new drugs. The Câmara de Regulação do Mercado de Medicamentos (CMED) is then responsible for approving the prices of new drugs despite the fact that there is limited government reimbursement. Drugs are classified according to one of six categories based on the degree of innovation and whether generics are available.

Prices of patented drugs are referenced against the lowest price in nine markets, comprising US, Canada, France, Italy, Spain, Portugal, Greece, Australia, New Zealand, and the country of origin. On application the CMED is obliged to give a pricing decision within 90 days for drugs in Categories I and II, and within 60 days for Categories III to VI, though it frequently takes longer than this stated time. After the price has been agreed upon, the CMED establishes permitted annual price increases each year (which do not apply to government and hospital purchases of drugs). In 2010, this price increase averaged 4.6%.

Prices of generics are required to be at least 35% lower than the price of original drugs, while branded generics have to be at the average price of branded and unbranded generics already on the market. In practice, depending on the number of generics competing on the market, generics usually sell at over a 50% discount to the price of the original product, while similares (branded generics which historically did not require proof of bioequivalence) are sold at a 60-70% discount. Doctors in the public healthcare system (known as SUS) are required to prescribe using generic names and generic substitution is allowed at the pharmacist level (between original and generic drugs but not similares). In practice, substitution with a similare frequently occurs at the patient's request (as they have to pay out of pocket) or as pharmacists seek to maximise profits by substituting with cheaper products where they have obtained larger discounts.

Unlike in many markets, the prices of many OTC medicines are tightly controlled, despite not being reimbursed. However certain products including analgesics and flu remedies can be freely priced. OTC medicines, like prescription drugs, are allowed annual price increases.

Russia

Russia represents a sizeable growth opportunity as the government addresses current poor (but improving) provision. However, its absolute potential contribution is limited by the relatively low population. To put this in context, with sales of $19bn in 2011, Russia ranks around 11th globally by pharmaceutical sales, just behind the UK, and its position is predicted to move up to 9th place by 2016 (source: IMS). An underdeveloped local market, coupled with mistrust of IP and government bureaucracy has led to the bulk of Russia's pharmaceutical spend (80%) being derived from imports. With currency swings this is simply too essential a sector to leave to external factors. As such the government has made clear its plans by 2020 to boost local production at the expense of imports. For now there is a credible growth opportunity for branded as well as OTC medicines from international pharmaceutical companies, but stated government favouritism for local producers means investments should be made with eyes wide open, and IP/know-how firmly locked away in home markets.

Pricing and reimbursement

In 2005 the government started a federal drug reimbursement program (called the Dopolnitel'noe Lekarstvennoe Obespechenie or DLO). This was later modified in 2008 into the ONLS programme (vulnerable people) and the "7 nosologies" programme (expensive disease programme):

- The ONLS programme provides reimbursement for drugs on the essential drug list for socially vulnerable people groups, e.g. disabled, veterans, and those affected by the Chernobyl accident. It is funded by the federal government and administered by regional governments through tender auctions.
- The 7 nosologies programme covers medicines for seven serious and expensive-to-treat diseases, namely leukemia, haemophilia, multiple sclerosis,

organ transplants, Gaucher's disease, Cystic fibrosis and growth hormone deficiency. Drugs purchased for the expensive disease programme are purchased by auction at the federal level by the Ministry of Health and Social Development and paid for by the federal government.

- Further to this, in April 2010, the Russian government implemented price controls on a list of medicines it deemed essential to its people (termed the Essential Drugs List or EDL). The list contains "Vital and Essential Pharmaceuticals" encompassing more than 5,500 products (30% of the Russian pharmaceutical market).

In Figure 115 below, we provide an introduction to the different market segments. Of note, retail pharmacies are the most common distribution channel for pharmaceutical products, accounting for 67% of sales. Conversely the government is the primary payor for segments amounting to 33% of pharmaceutical sales through its involvement in hospitals (14%), ONLS (11%) and expensive diseases (8%).

Figure 115: Description of different market segment

	Retail	ONLS (vulnerable people)	7 diseases (VZN program)	Hospital
Description	Retail pharmacy sales, comprising prescription and OTC	State program covering c.5.7m people who receive social assistance, e.g. veterans, disabled	State program covering c.66,000 patients with seven expensive to treat diseases	Hospital sales
Market share	67%	11%	8%	14%
Prescription	Doctors/patients	Doctors	Doctors	Doctors
Dispensation	Pharmacies	Pharmacies	Pharmacies	Hospitals
Pricing	Free, except for drugs on EDL	Regional tender	Federal tender	Tender
Funding	80-90% of outpatient expenditure paid out-of-pocket, i.e. OTC and non-reimbursed Rx	Federal	Federal	Federal

Source: Deutsche Bank

India

India represents a market of significant potential. With sales of around $13bn in 2011 it ranks around 13th globally by pharmaceutical sales, two places behind Russia, but is expected to leapfrog the latter to attain 8th place by 2016, according to IMS. However, weak IP enforcement and a strong low-priced local branded generics market make it unattractive to many multinational pharmaceutical companies in the short to medium term. We expect local companies to be the primary beneficiaries in this market during this period. However, with gradual improvements in intellectual property for new innovative products, we believe international companies with stocked pipelines and new innovative drugs stand to benefit in this market over a longer term horizon relative to those that choose an undifferentiated strategy.

Pricing and reimbursement

Pricing of pharmaceuticals is essentially uncontrolled in India (exception for 74 molecules on government formularies) and reimbursement is rare with most medicines paid for out-of-pocket. Payers (individuals, but also states, local governments, hospitals) lack size, organisation and negotiating power to impose prescribing controls or formularies, leaving the prescribing decision firmly in the hands of the treating physician and the ability of the patient to pay for his/her treatment.

In the hospital setting, physician's choice and the availability of products in the hospital pharmacy as well as insurance/ability to pay are key to the prescribing decision. Where formularies exist, doctors still play a major role in the listing decision. Over the long

term we expect hospital formulary decisions to play a greater role than at present (but with no specific, nor near-term timeline).

The Ministry of Health and Family Welfare (MOHFW) oversees drug approvals. Within this the Drugs Controller General of India (DCGI) has taken over approval responsibility for the individual states (since 2009). Approval of drugs is based on the clinical application and is completely independent of the patent process. Thus multiple copies of originator brands can be approved. The patentability, infringement and action course thereof has to be tackled separately through the courts.

The Indian government has historically been slow in enforcing intellectual property (IP) rights, with many domestic pharmaceutical companies building their reputation (and business) from manufacturing cheap generic versions of patented drugs. In January 2005, India signed up to the World Trade Organization's Trade-related aspects of intellectual property rights (TRIPS) agreement, which formally recognizes pharmaceutical patents (i.e. product patents rather than only manufacturing process patents that are easily navigable). While this has improved the situation for multinationals, enforcement of IP rights continues to be an issue. Pharmaceutical companies face potentially long delays in patent applications and court proceedings and - even when a case has gone to trial - the courts may merely require generic manufacturers to compensate the patent holder without requiring the generic company to cease production or sale of the unauthorised copy.

Given current IP protection, marketing branded generics represents a winning strategy in India. However, the TRIPS agreement has encouraged some pharmaceutical companies with productive pipelines to launch innovative drugs (albeit limited thus far). We expect this segment of the market to grow over the longer term and as such expect India to become more attractive to companies with innovative pipelines (e.g. Novartis, Roche). However, we do not see it yet as a significant opportunity given the pace of new drug launches, the small proportion of people able and willing to pay for innovative products and the likely continued challenges and lack of IP enforcement.

Consumer healthcare

- 'Consumer healthcare' spans a range of personal care and health-related categories.
- Global sales of over-the-counter medicines sub-category was $78 billion in 2011.
- Leading consumer healthcare companies include Proctor & Gamble, Johnson & Johnson, Colgate-Palmolive and GlaxoSmithKline.

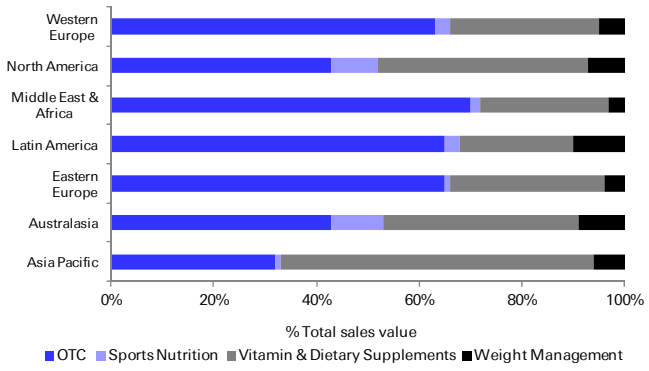
In recent times, the larger pharmaceutical companies have in many cases attempted to diversify their business away from a dependency on the 'boom-and-bust' cycle of blockbuster drugs and thereby to reduce volatility of earnings. One such strategy has been to diversify into the consumer healthcare business. This loosely defined business category straddles a broad range of consumer goods and personal health products which rely for their longevity and profitability on brand power, backed by consumer-led sales and advertising.

Consumer health market

The definition of consumer healthcare varies from company to company. In its broadest sense it comprises any consumer goods category in which health or welfare claims can be made. Key segments include over-the-counter (OTC) medicines, personal hygiene, oral care, food & beverage/nutritional products, women's health, and infant care products. Novartis also includes its animal health activities under this broad heading. (We discuss animal health separately in the next section). Many leading products are well-recognised brands, which one would associate with a fast-moving consumer goods company rather than a pharmaceutical company, e.g., Ribena (GlaxoSmithKline), Dr. Scholl (Merck), Neutrogena (Johnson & Johnson). Though there is an argument to be made for the sale or spin-off of these brands given the lack of synergy with the core pharmaceuticals business (other than over-the-counter medicines; discussed separately below), there is much brand equity in these products and benefits in being associated with them. Operating margins average 15-20% for this sector which, while low compared to prescription pharmaceuticals, are nevertheless relatively attractive and also defensible due to customer loyalty and marketing.

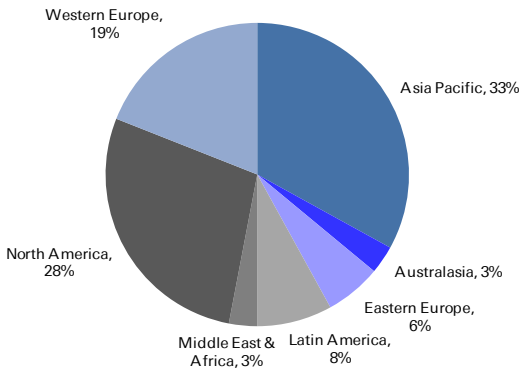
Over-the counter (OTC) drugs comprise the largest portion of the consumer health market by sales, closely followed by the vitamin and dietary supplements market (Figure 116). Given the diversity in consumer healthcare, we will not discuss this further, bar OTC medicines, which share synergies in production and life-cycle management of medicines.

Figure 116: Composition of consumer health sales, 2011



Source: Euromonitor

Figure 117: Global consumer health sales by region, 2011



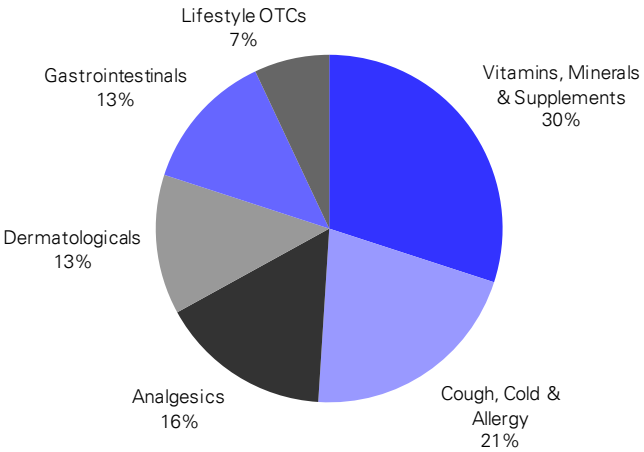
Source: Euromonitor, Deutsche Bank

Over-the-counter drugs

The one segment which may potentially provide clear synergies with the pharmaceuticals business is the over-the-counter drugs (or OTC medicines) segment. OTC medicines are those that can be purchased by the consumer without a prescription, and are usually distributed through pharmacies, grocery stores and convenience stores. They are usually older drugs which have lost patent protection and have been deemed safe for consumption without a physician's review. Marketing is done directly to the consumer via TV, web and publication-based advertising. Brand awareness is crucial, as these drugs are usually sold at a premium – even though they may be placed next to identical generic copies on the pharmacy shelf.

Kalorama Information estimates that global OTC sales totalled $78 billion in 2011, growing at a CAGR of 3.5% pa over the previous three years. The top ten companies in this category account for only about one-third of sales and, geographically, the US is the largest OTC medicines market. The biggest selling OTC categories are: vitamins, minerals and supplements; cough, cold and allergy products; and pain-relieving medications (analgesics).

Figure 118: Breakdown of six leading US OTC categories by sales



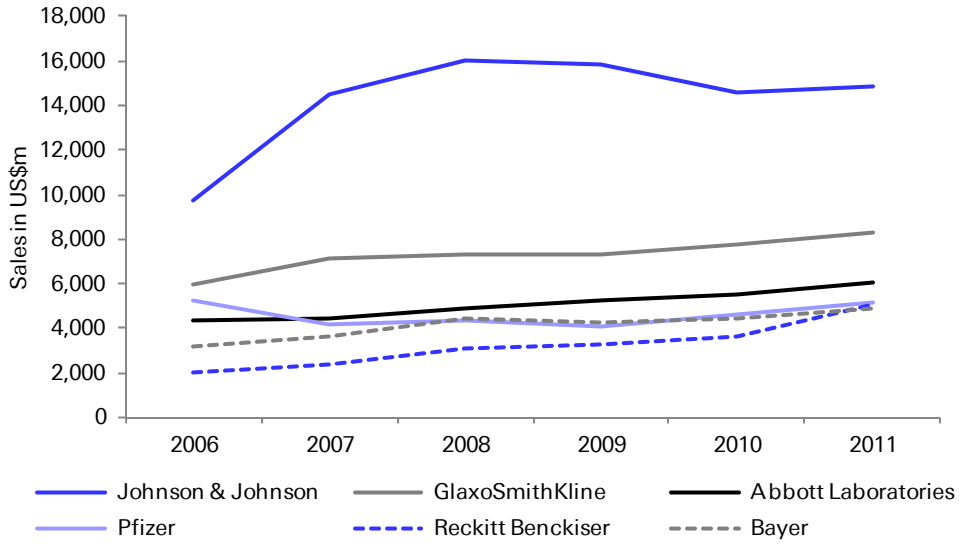
Source: DB Hall's DB6 – 2008, Sanofi presentation during acquisition of Chattem

To be taken OTC, a medication must be 'switched' from prescription-only status. In the US, the approval of OTC drugs is handled by the FDA's Centre for Drug Evaluation and Research. As there are many producers of the same drug, the FDA regulates the active ingredients and their labelling, rather than the individual products. For each drug, an OTC drug monograph is prepared and filed in the Federal Register, which contains the approved active ingredient, dosages, formulations and labels. Once the monograph is in place, companies can then register to sell the OTC product without requiring additional FDA pre-approval.

In the EU, to receive approval for conversion into an OTC drug, an application needs to be filed with the European Medicines Agency. If there is no change to a drug which has already received marketing authorization from the EMA, then a Type II variation application can be filed to amend the classification. Otherwise, a new application for marketing authorization is required. The drug company should also submit additional data demonstrating the drug's track record and safety, and if approved, the company will have data exclusivity for the new data for up to a year.

Sales

Figure 119: Sales of consumer healthcare products by pharma companies



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 120: Sales of consumer healthcare products ($ m) by pharma companies

	2006	2007	2008	2009	2010	2011
Johnson & Johnson	9,774	14,493	16,054	15,803	14,590	14,883
GlaxoSmithKline	5,921	7,113	7,351	7,316	7,746	8,331
Abbott Laboratories	4,313	4,388	4,924	5,284	5,532	6,006
Pfizer	5,239	4,179	4,354	4,111	4,639	5,195
Reckitt Benckiser	1,987	2,400	3,114	3,253	3,584	5,061
Bayer	3,180	3,612	4,438	4,293	4,473	4,919

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Animal health

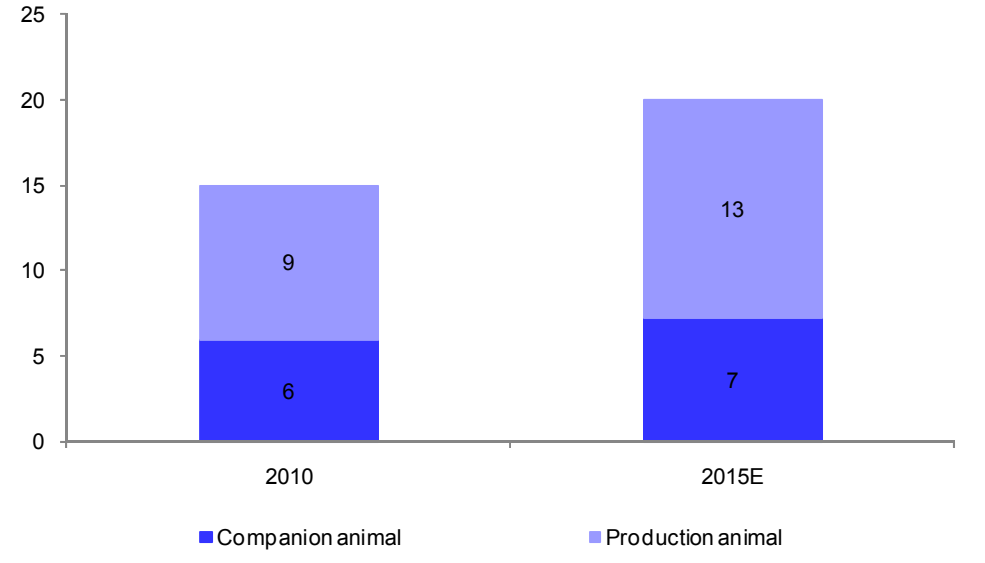
- Global sales in the animal health market are in excess of $18 billion (€15 billion) pa
- Mid-high single digit historic growth; Vetnosis projects 5% CAGR to 2010-15.
- Sales of AH products split roughly into 60% production animals, 40% companion animals.

The Animal Health (AH) market includes the supply of medicines, vaccines and healthcare products to vets, farmers and animal owners. This business can be complementary with human healthcare as a number of products, notably in the anti-infective field but also to a growing degree in metabolic products (eg, drugs for high blood pressure), can find application across species. Furthermore many medicines have already been tested in animals prior to approval in man. The two main target markets are companion animals (pets) and production animals (cattle, poultry, sheep and swine). The principal drivers of demand are the growing global population, rising incomes applied to pets (as a result of ageing populations in the West and higher incomes in the emerging markets, or EMs) and the increasing consumption of animal protein in EMs.

Animal health market

The market was worth €15 billion in 2010, according to industry consultants Vetnosis, and has historically grown in "mid-high single digits", according to Sanofi. While certain product areas within AH are more sensitive to global economic conditions (eg, companion animals), underlying market demand has continued to grow through the financial crisis. Looking forward, Vetnosis projects that the market will grow by a 5% CAGR in each major category to 2015E (Figure 121), so that the overall AH market reaches €20 billion.

Figure 121: AH market by sales, 2010-15E (€ billion)

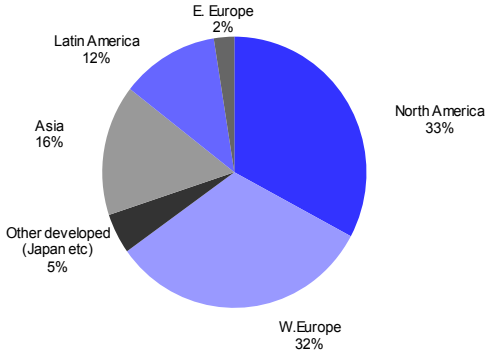


Source: Sanof, Vetnosis, Deutsche Bank

Sales of AH products split roughly into 60% production animals, 40% companion animals. The biggest product categories are anti-infectives (parasiticides) and vaccines,

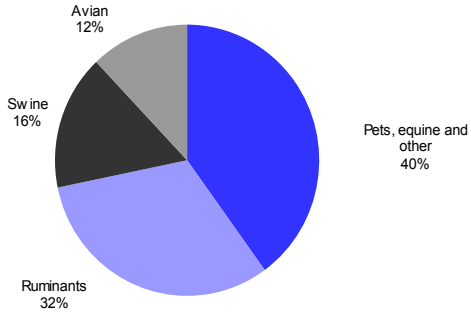
which together account for just over half of sales. By far the biggest geographic markets are North America and Western Europe, which account for two-thirds of global sales. EMs account for c.31% of the market: this is expected to rise to c.36% by 2015 (based on a projected 2010-15E sales CAGR of 8% versus 4% for developed markets).

Figure 122: Sales by region (2010)



Source: Sanofi, Vetnosis, Deutsche Bank

Figure 123: Sales by animal category (2010)

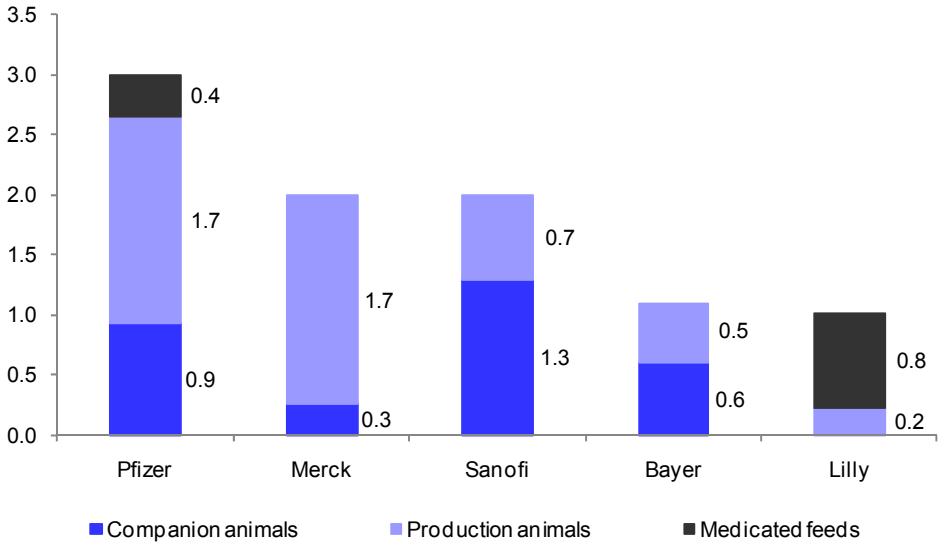


Source: Sanofi, Vetnosis, Deutsche Bank

The companies

The top five companies account for approximately 60% of the AH market (Figure 124). In descending size order these are Pfizer (c.20% share), Merck/ISP (13%), Sanofi/Merial (13%), Bayer (c.7%) and Lilly/Elanco (7%). The other major EU player is Novartis, which ranks seventh (with a c.6% share). Note that a planned merger of Merck's and Sanofi's AH businesses was abandoned in March 2011 as the anti-trust mandated divestment requirements were too onerous.

Figure 124: Leading players in AH, based on 2010 sales (€ billion)

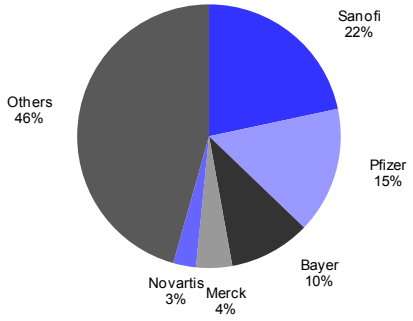


Source: Sanofi, Vetnosis, Deutsche Bank

The profiles of the leading companies vary significantly by category. As can be seen in Figure 125 and Figure 126, Sanofi leads the companion animal category with Pfizer a strong second, Bayer in third place and others trailing with much smaller shares. Over

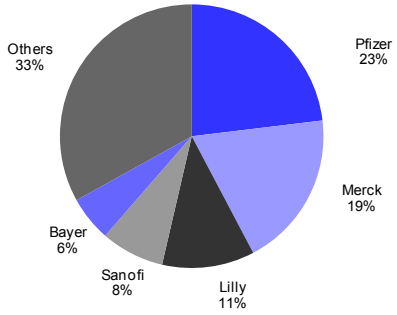
half of Sanofi's position in this category comes from the Frontline family of pet parasiticides, which is the largest product franchise in AH (2011 sales: €764m). Bayer's Advantage line of pet parasiticides (2011 sales: €420m) also occupies a major position in companion animals. In production animals, by contrast, Pfizer and Merck are the clear leaders, with Lilly a strong third (Lilly's position is mainly by virtue of its medicated animal feed additive business rather than traditional drugs and vaccines).

Figure 125: Companion animal category (€6bn)



Source: Sanofi, Vetnosis, Deutsche Bank

Figure 126: Production animal category (€9bn)



Source Sanofi, Vetnosis,: Deutsche Bank

Why is the Animal Health market attractive?

The unsuccessful merger of Sanofi's and Merck's AH units and the expressions of interest by other companes in Pfizer's AH unit (which has been under review by the company and is now in planning for a partial IPO) raise the valid question of why this market is deemed so attractive by certain healthcare industry participants. While it is likely the case that some of the M&A ambitions displayed by the smaller AH players are partly defensive in nature, given the competitive strengths of the largest companies, we believe the market is fundamentally attractive in its own right for several reasons:

- The **complex regulatory environment** creates a major barrier to entry, with multiple agencies involved. These include the regulators (eg, FDA's Center for Veterinary Medicine, EU Commission), which impose similarly extensive data requirements to those required for registration of human medicines. Additionally, however, certain AH categories are regulated in the US by the Environmental Protection Agency and vaccines are under the control of the US Department of Agriculture. Food safety bodies may also have an oversight role.
- **Demand prospects are solid**, driven by companion animals being increasingly treated as family members and by increased protein consumption (the latter driven by demographic trends and rising living standards). These factors are of course likely to be most evident in EMs, hence the expectations for faster growth in the developing world than in the US and Western European markets.
- **Product life cycles are long and generic competition is limited** compared with human pharmaceuticals. This reflects the fact that distribution is largely to veterinarians or veterinary wholesalers with a virtual absence of third party payers. Thus a survey of the top 50 compounds in the industry has shown that pioneer brands have an average age of 30 years and – even after facing generic competition – retain a 60% average share (source: Vetnosis). A recent example is Merial's Frontline: here the product's EMEA sales dipped by less than 10% when branded generic competition arrived after the 2009 EU patent expiry.

- Following on from this, **brand equity and brand loyalty is very important** in AH and many of the products have characteristics much more in keeping with over-the-counter/consumer healthcare brands than with prescription drugs.
- Clear **synergies** exist for those companies with human healthcare activities, notably in R&D. Novartis, for example, has stated that a third of its R&D pipeline in AH consists of projects derived from its human health pipeline.
- The probability of success and **cost of R&D is lower than in human healthcare**. For example, Merial has a large new product pipeline (27 launches planned over 2011-15E, six already achieved) and yet its R&D/sales ratio of 7.2% is under half that of Sanofi's prescription (14.7%) and vaccine (16.3%) units.
- In certain AH product categories, **manufacturing complexity** offers an additional barrier to entry. This particularly applies to vaccines and other biological products.

Finally, **profitability is attractive** and closer to that of prescription pharma (typically 30-40%) than consumer healthcare (15-20%). Merial reported a 31% operating margin in 2011 and Bayer has stated that its AH unit enjoys "industry-leading profitability", suggesting that it at least matches Merial.

Vaccines

- Global sales of vaccines totalled $25 billion in 2011.
- Oligopolistic market structure, with five main players (GlaxoSmithKline, Sanofi, Merck, Pfizer and Novartis) and high barriers to entry.
- Vaccines grew at 12% CAGR over past 5 years, Sanofi projects 6-7% annual growth to 2015.

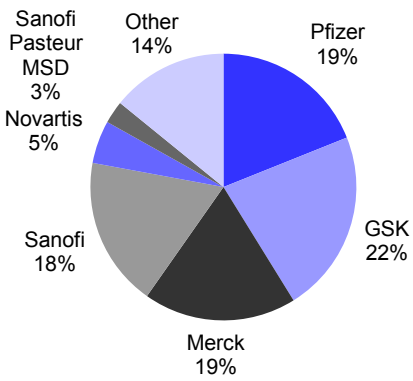
Introduction

From the serendipitous discovery by Edward Jenner of the first vaccine for smallpox in the 1790s, our understanding and application of vaccination has extended to cover a spectrum of illnesses. National childhood immunization programs are widely prevalent in both developed and developing countries, and account for the large strides in reducing infant and childhood mortality over the past century. In fact, thanks to a concerted global immunization program, debilitating diseases such smallpox and polio are now considered a thing of the past. In a testament to the possibilities of such programs, the World Health Organization declared smallpox to be officially eradicated in 1979. Most countries' immunization schedules now usually include vaccination against tuberculosis, pertussis, diphtheria, polio, tetanus, measles, mumps, rubella and hepatitis B. More recently, vaccines for viruses such as HPV, herpes zoster and rotavirus have been launched. Annual vaccinations against influenza have also gathered greater emphasis in light of the recent avian and swine flu pandemic scares.

The companies

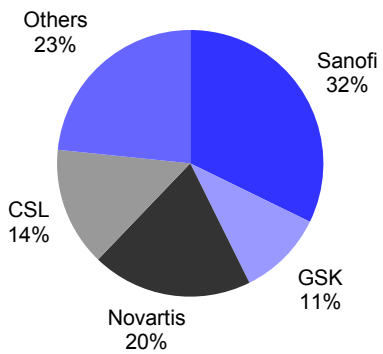
The vaccines industry is an oligopoly, with high hurdles to entry in the form of manufacturing complexity, technical know-how, strict regulatory oversight and heavy capex requirements. Currently, five global companies dominate this industry (note that Sanofi Pasteur MSD is a European joint venture between Sanofi and Merck).

Figure 127: All vaccines, 2011



Source: Deutsche Bank, EvaluatePharma

Figure 128: Influenza vaccine sales, 2011



Source: Deutsche Bank, EvaluatePharma

Methods of vaccination

Vaccination is a process where a substance is introduced to the body to stimulate an immune reaction, conferring immunity to the disease. This may be done via several methods.

Inactivated vaccines

This method uses an inactivated (or killed) version of the active pathogen/virus, which is rendered inactive but still retains the ability to be recognised by the immune system. Examples of this include the influenza and cholera vaccines.

Attenuated vaccines

This method is to use a live but weakened (attenuated) form of the virus, which has been specially cultivated to reduce its disease-causing properties, but is still alive and able to cause mild infections. This method usually results in a longer-lasting immunity, and examples of this category include the mumps and rubella vaccines.

Subunit vaccines

For certain vaccines, rather than using the whole virus, a specific antigen or protein from the viral coat is selected and used to incite an immune response. This is sufficient to protect against an infection by the whole virus, and an example of this method is the Hepatitis B vaccine, which uses the Hepatitis B surface antigen.

Toxoid vaccines

In this instance, toxins produced by the pathogen (usually bacteria) are inactivated and form the basis of the vaccine. Examples of this include the tetanus and diphtheria vaccines.

Conjugated vaccines

In the instance where the protein is poorly antigenic (i.e., not easily recognised by the immune system), it can be attached to a protein, which facilitates recognition by immune cells. Examples include the two commercially available conjugated pneumococcal vaccines – Prevnar and Synflorix.

Pharmacological treatment

Though there are a variety of vaccines available, it is helpful to divide this market into several segments.

Influenza

Flu is not caused by just one virus, it is in fact caused by many different strains of a virus, the most prevalent forms of which vary from year to year. The World Health Organization runs a Global Influenza Surveillance Network, that monitors the strains of flu virus prevalent globally. It then predicts the dominant strains of influenza likely to spread during winter and recommends those strains to be incorporated into the respective Northern Hemisphere and Southern Hemisphere influenza vaccines. Additionally, in 2009, vaccines were produced by special request for governments around the world in response to the H1N1 “swine” flu pandemic.

Figure 129: Leading influenza vaccines

Name	Generic	Company	2011 ($m)
Fluzone/Vaxigrip	influenza vaccine	Sanofi	1,150
FluLaval/Fluviral	influenza vaccine	GlaxoSmithKline	369
Fluvirin	influenza vaccine	Novartis	364
Celtura	swine (H1N1) influenza vaccine	Novartis	362
Afluria	influenza vaccine	CSL	283
Panvax H1N1 Vaccine	swine (H1N1) influenza vaccine	CSL	280
Influvac	influenza vaccine	Abbott Laboratories	198
H1N1 HA flu vaccine	swine (H1N1) influenza vaccine	Mitsubishi Tanabe Pharma	186
Fluzone ID	influenza vaccine	Sanofi Pasteur MSD	183
FluMist	influenza vaccine	AstraZeneca	161
Influenza A (H1N1) Vaccine	swine (H1N1) influenza vaccine	Sanofi	107

Source: Company data, EvaluatePharma, Deutsche Bank estimates

Infant and paediatric

Each country has its own national immunization schedule, which varies according to the diseases endemic to their region and what is determined to be cost-effective. However, several vaccines are almost universally included, such as polio, measles, mumps, rubella, tetanus, tuberculosis, diphtheria, pertussis and Hepatitis B. Human papillomavirus (HPV) vaccines have increasingly been incorporated into immunization schedules of developed countries in recent years and are considered here, even though they are administered in an older age group (typically teenage/adolescent girls). The pneumococcal, meningococcal and rotavirus vaccines are also popular vaccines for infants, and have been incorporated into the immunization schedules of some developed countries. In view of the sheer number of vaccines administered under the age of two, an important development has been the creation of multi-valent vaccines, which immunize against a number of diseases in a single vaccination, e.g., Sanofi's pentavalent vaccine Pentacel and GlaxoSmithKline's Pediarix.

Figure 130: Leading children's vaccines

Name	Generic	Company	2011 ($m)
Prevnar 13	pneumococcal vaccine	Pfizer	3,657
PENTAct-HIB	DTPw, Hib & polio vaccine	Sanofi	1,496
Gardasil	human papillomavirus (HPV) vaccine	Merck & Co	1,209
Pediarix	DTP, hepatitis B & polio vaccine	GlaxoSmithKline	1,106
Varivax	varicella vaccine	Merck & Co	822
Cervarix	human papillomavirus (HPV) vaccine	GlaxoSmithKline	811
RotaTeq	rotavirus vaccine	Merck & Co	651
Menactra	meningococcal A, C, W-135 & Y vaccine	Sanofi	594
Synflorix	pneumococcal vaccine	GlaxoSmithKline	561
Pneumovax 23	pneumococcal vaccine	Merck & Co	498
Prevnar	pneumococcal vaccine	Pfizer	488
Rotarix	rotavirus vaccine	GlaxoSmithKline	481
Adacel	DTPa vaccine	Sanofi	437

Source: Company data, EvaluatePharma, Deutsche Bank estimates

Infectious diseases

This last group encompasses the remaining vaccines which protect against certain diseases, but have not been universally recognised in immunization schedules. These tend to be country-specific and recommended in travel advisories, e.g. yellow fever and tick encephalitis vaccines, or more lifestyle vaccines, e.g., varicella (chicken-pox).

Figure 131: Leading disease vaccines

Name	Generic	Company	2011 ($m)
Hepatitis Vaccine Franchise	hepatitis A & B vaccine	GlaxoSmithKline	1,103
Varivax	varicella vaccine	Merck & Co	822
Zostavax	herpes zoster vaccine	Merck & Co	332
Recombivax HB	hepatitis B vaccine	Merck & Co	171
Jebik V	japanese encephalitis vaccine	Mitsubishi Tanabe Pharma	114
TBE Vaccine	tick-borne encephalitis (TBE) vaccine	Baxter International	105

Source: Company data, EvaluatePharma, Deutsche Bank estimates

Clinical end-points

As preventative agents, one measure of effectiveness is the percentage of vaccinated patients who subsequently develop the illness in question. However, many childhood diseases, though life-threatening, are thankfully not common. Hence, a lack of disease may not be an accurate measure of effectiveness. The most common measure in these instances is an assessment of serum antibodies against the various diseases as a proxy for immunity. Diagnostic tests are frequently conducted about a month after the last dose of the vaccine to measure the antibody response against the different antigens.

Pipeline products

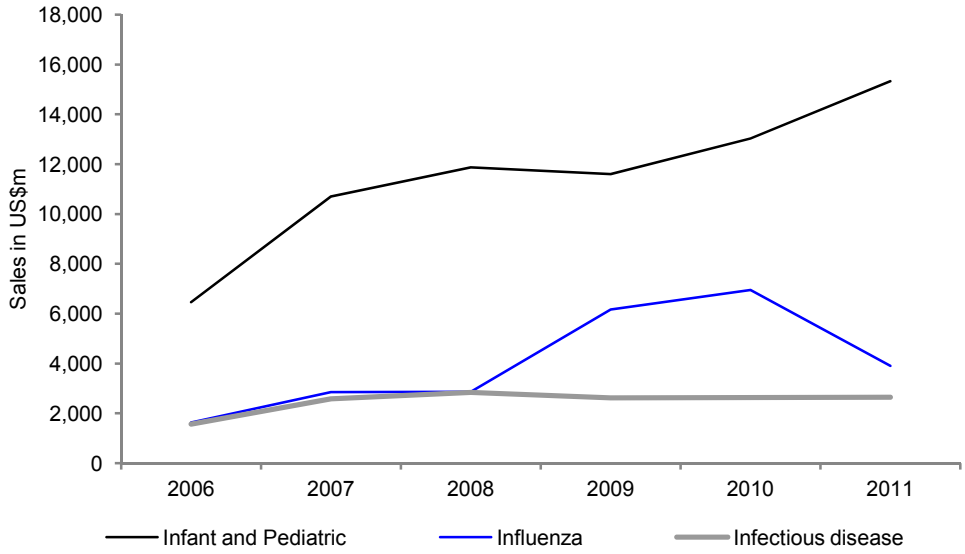
There has been a renewed interest in vaccines research in recent years, and the vaccine development pipeline has several interesting new therapies in late-stage development. Vaccines are now available for most of the childhood diseases in developed countries and the quest is now on for childhood diseases which may be rarer but are associated with devastating consequences. For example, one of the higher profile vaccines in late-stage development, Novartis' MenB vaccine, Bexsero, has been developed to protect infants against meningitis B virus, the most common cause of viral meningitis in children in Europe and places outside the US. It is currently under regulatory review in Europe and a scientific opinion is expected in 4Q 2012.

Another focus of pipelines is vaccines for the developing world. This is in part supported by substantially improved funding (including by supra-national organizations such as The Global Alliance for Vaccines and Immunisation (GAVI) and the Pan American Health Organization (PAHO). Novel vaccines are in development respectively by Sanofi and GlaxoSmithKline for two of the most devastating endemic diseases, dengue fever and malaria. The vaccines concerned are each undergoing Phase III studies, which are schedule to complete in 2014 and 2016 respectively. Vaccines are also in development that seek to reduce the burden of childhood vaccination schedules, which is particularly important in regions where access to healthcare is more complex.. An example of this is Hexaxim, Sanofi's liquid hexavalent vaccine, which will be the first product to protect against six childhood diseases in a single injection (diphtheria, tetanus, pertussis, hepatitis B, polio and Hib) and is largely targeted at the developing world.

Finally, while not a vaccine in the strictest sense, Dendreon's Provenge was the first vaccine approved for the treatment of cancer in 2010. More appropriately called immunotherapy (as it aims to treat the disease rather than prevent it), the production of Provenge involves a lengthy, expensive process of extracting the body's immune cells, stimulating them to attack the cancer cells, and infusing them back into the body. However, Dendreon has faced numerous operational and logistical issues in scaling up production of Provenge, illustrating the technical challenges involved for such

treatments. Still, the product remains an important proof of concept and may open the door to "therapeutic vaccines" for other cancers in the future. GlaxoSmithKline, for example, has such a vaccine, called MAGE-A3, in Phase III trials for the treatment of non-small cell lung cancer and melanoma (data expected 2013).

Figure 132: Sales of vaccine categories



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 133: Sales of vaccine categories ($ m)

Category	2006	2007	2008	2009	2010	2011
Infant and Pediatric	6,456	10,703	11,868	11,606	13,028	15,326
Influenza	1,627	2,854	2,871	6,167	6,954	3,902
Infectious disease	1,567	2,588	2,843	2,621	2,636	2,647

Source: Company data, Deutsche Bank estimates, EvaluatePharma

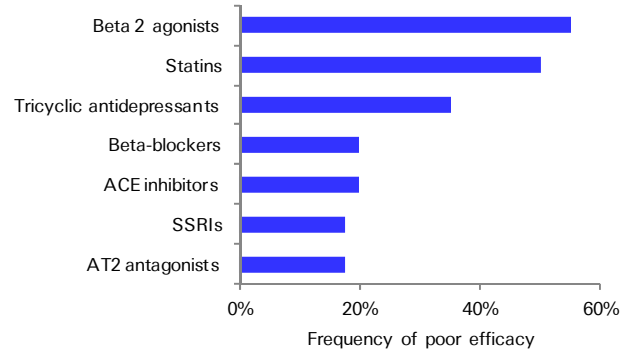
Companion diagnostics

- Roche estimates the in vitro diagnostics market was $44bn in 2010.
- 50% of drugs in early stage clinical trials rely on biomarker data.
- The FDA plans to release final guidelines for companion diagnostics in 2012.

Molecular diagnostics

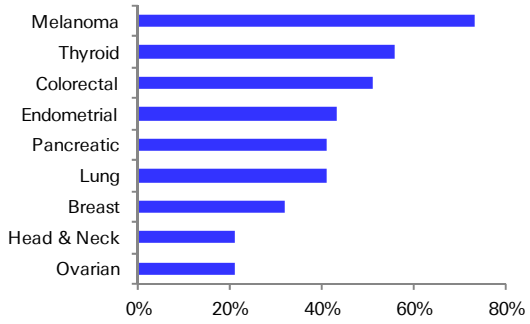
Companion diagnostics are personalised molecular diagnostic tests and constitute a significant branch of the evolving paradigm of personalized medicine, which aims to customize therapy based on the genetic composition of each individual or the composition of their disease-causing cells. Individuals have varying responses to treatments due to differences in the way their body metabolises drugs (pharmacokinetics, involving absorption, metabolism, distribution and excretion) and the differences in how drugs affect the body (pharmacodynamics). Pharmacogenomics seeks to explain the correlation between drug response and genetic variation. Studies suggest that in most cases, less than half of pharmacological treatment is effective (Figure 134).

Figure 134: Poor efficacy is often seen even with common drug classes



Source: Roche, genes and health, Deutsche Bank

Figure 135: Percent of cancers where specific mutations can be detected and targeted by drugs



Source: Wall Street journal

Increasingly, newer therapies are being developed to act on specific targets at a molecular level. Molecular diagnostics encompass laboratory tests used to screen for the presence of these target sites to identify patients that may be more likely to benefit from a targeted therapy. The objectives of integrating them into traditional treatment include predicting efficacy and reducing exposure of non target patients from potentially harmful drug side effects. This also theoretically will benefit healthcare costs and allow companies to price drugs higher due to their improved reward-risk utility. The most frequent application is in oncology, where cancer cells are frequently marked by the presence of a distinctive protein (eg. HER2 in certain breast cancers). Companion diagnostics are also useful for drugs that may have serious side effects in people with certain mutations and cannot be safely prescribed without testing. In addition, selective treatment helps decrease the likelihood of ineffective therapy and could soon become a necessity, as governments and payors alike look for ways to lower healthcare costs.

Types of biomarker

The delivery of personalized healthcare through molecular diagnostics is based on the detection or monitoring of disease specific biomarkers, which may be related to variations in DNA or may be proteins found in human tissue. A biomarker can be any protein in the body that signals the presence or status of disease activity. For example, the presence of a specific bacterial antibody in body fluids indicates current or past exposure to the bacterial antigen.

DNA biomarkers are most frequently employed in oncology, as mutations in gene expression are often related to the development of specific cancers. For example, over-expression of the gene that encodes HER2 results in a more aggressive form of breast cancer, mutation of the KRAS or p53 genes are linked to development of various cancers, mutations affecting EGFR expression have also been linked to various cancer types. Biomarkers can be divided into four categories, with some overlap.

Screening markers

These tests are applied to large groups of people to detect disease before it is clinically apparent, or to screen for specific traits. Screening tests should ideally be minimally invasive, easy to administer and economical. Examples include screening for anemia in potential blood donors.

Prognostic markers

Once disease has been diagnosed, prognostic markers can be used to monitor the rate of progress of the disease. These biomarkers guide physicians on the correct choice of therapy and also helps identify a recurrence of the disease. This category predominantly comprises tumor markers which also play a role in diagnosis. Examples include prostate specific antigen (PSA) levels in prostate cancer and CA125 in ovarian cancer.

Stratification markers

Stratification markers help physicians identify patients that are more likely to respond to a specific therapy, or that may potentially experience dangerous side effects. For example, patients who metabolise drugs faster may require higher doses while slow metabolisers may have a higher incidence of side effects and hence need lower doses. Such variations can be detected using modern diagnostic tests. Drug response may also depend on the activity of a specific target. For example, Herceptin is designed to treat patients with breast cancer which express the HER2 protein. Another example is the JCV virus assay, which screen patients with multiple sclerosis prior to commencing treatment with Tysabri, to reduce the risk of developing PML. Stratification markets may also help physicians prognosticate the disease. For example, an infection with genotype 1 of the hepatitis C virus is associated with more persistent disease and requires a more aggressive approach to treatment from the onset.

Efficacy markers

As implied, efficacy biomarkers indicate effectiveness of therapy in controlling disease progress, both prior to and during treatment. Most tumor markers in oncology also serve as efficacy markers.

Co-development of drugs and diagnostics

Role of regulatory bodies

The cost of sequencing the human genome has declined from nearly $3bn in 2003 to less than $5,000 in 2011, enabling the application of personalized healthcare in practical medicine. The FDA has also encouraged the development of companion

diagnostics and released draft guidance in July 2011 providing for simultaneous development and approval of companion diagnostics with their therapeutic counterparts. This is positive as therapies and their companion diagnostics were previously reviewed separately, hence presenting a risk should either be rejected or delayed. The guidance also allows for cross-labelling the drug and the diagnostic test. The concurrent review process not only allows optimisation of FDA resources, but also helps drug manufacturers as they can launch and market the drug-diagnostic combination without additional expense.

The FDA regulates and encourages the use of companion diagnostics to optimize therapeutic outcomes where the diagnostic test has a clear and demonstrable correlation with the mechanism of action of the drug. The most common drug candidate for a companion diagnostic is one that is effective contingent on the presence/activity of a receptor/mutation in the patient (Figure 136 lists some examples of such drugs). Developing companion diagnostics concurrently with drugs allows more efficient patient selection for clinical trials; a higher probability of a successful outcome, lower number of participants in trials, faster drug time, and a lowering of drug development costs.

Figure 136: Cancer treatments with specific targets

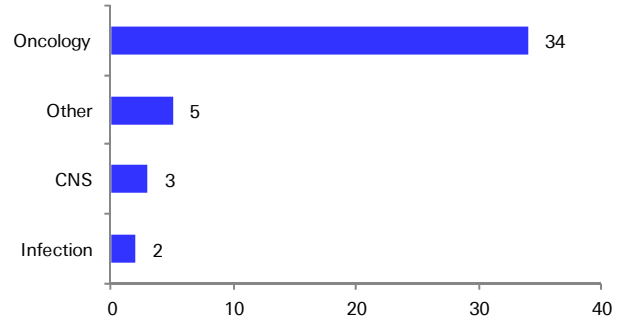
Cancer	Target	Drug
Breast	Estrogen receptor	Tamoxifen
Breast	HER-2	Herceptin, Tykerb
Chronic lymphocytic leukemia	CD-20	Rituxan/Mabthera
Non small cell lung cancer, colorectal, ovarian and renal cell cancers	VEGF	Avastin
Colorectal cancer	EGFR	Erbitux
Gastrointestinal stromal tumour, chronic myelogenous leukemia	C-KIT	Gleevec
Lung cancer	EGFR	Tarceva, Iressa
Melanoma	RAF	Zelboraf

Source: Deutsche Bank, ecancermedicalscience

Increasing pharma-diagnostic partnerships

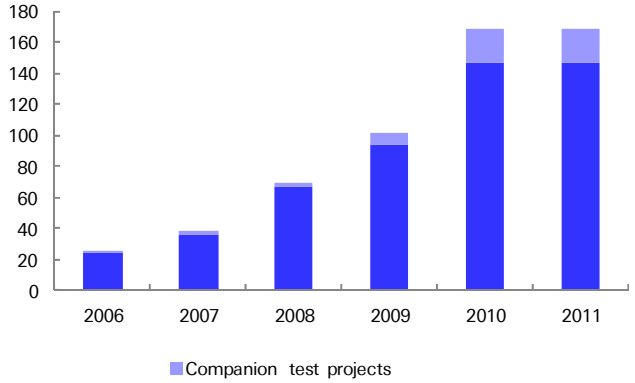
In practice, drug developers and diagnostic manufacturers have recognised the economic opportunity in co-development and the number of partnerships has grown (Figure 137 and Figure 138). To further optimize costs, Roche has integrated drug development in its pharmaceutical division with its diagnostic division, while Novartis has established a molecular diagnostics division and launched a biomarker discovery program within its pharmaceutical division, aided by the acquisition of Genoptix.

Figure 137: Number of partnerships between Pharma companies and companion diagnostics, 2009-10



Source: PricewaterhouseCoopers, Diagnostics 2011

Figure 138: Collaborations between Roche Diagnostics and Pharmaceuticals



Source: Roche personalized healthcare

Other applications of personalized medicine in diagnostics

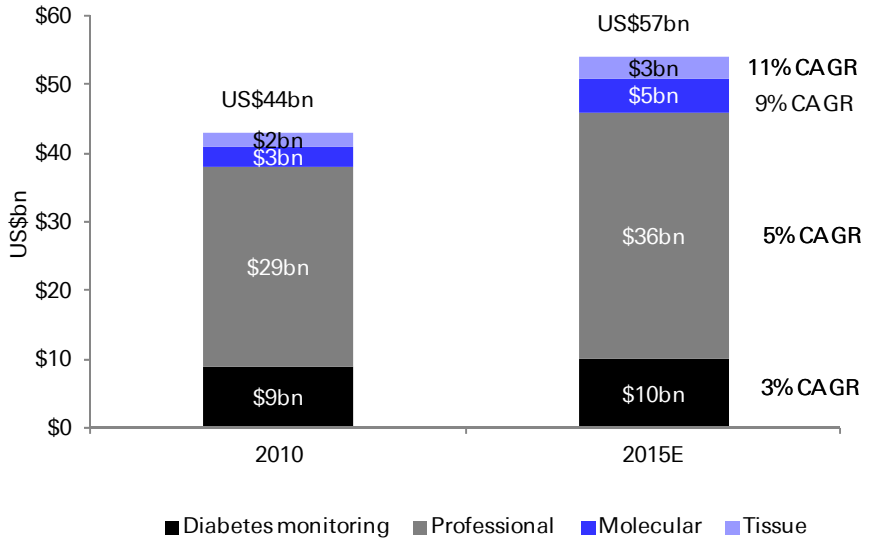
The role of diagnostics in personalized healthcare goes beyond their application in treatment selection. The highest selling personal diagnostic devices are blood glucose monitors, which help diabetes patients self-monitor their blood glucose levels through convenient and minimally invasive methods. These devices comprise c.85% of the biosensor market. Recent advances propose to elevate these to the potential of companion diagnostics, by combining continuous glucose monitoring devices with insulin delivery devices that automatically adjust insulin dosage based on blood glucose levels. Similar devices also allow patients on blood thinners to monitor their blood coagulation status, thereby enabling them to reduce the incidence of the unwanted side effect: bleeding events. Newer research is focused on developing tests that are non-invasive and can process results in a short time. These could be crucial in developing countries, where healthcare networks are poorly developed and infectious disease is a major cause of mortality.

Economic benefit

As we previously saw in Figure 134, often times the drugs prescribed to patients are ineffective; this has repercussions for all stakeholders: patients, physicians, payors, governments and drug companies. According to a 2005 Frost & Sullivan estimate, the cost of developing a companion diagnostic averaged roughly $40 million, a mere fraction of the $1.2bn involved in developing a new drug, offering a compelling risk-reward for pharmaceutical companies bearing the cost of development. While the use of companion diagnostics could directly create savings for global healthcare systems through a decline in ineffective prescriptions, there is also an indirect benefit on quality of life for patients who might otherwise experience distressing side effects while receiving ineffectual therapy.

The personalized medicine coalition estimates that though only 1% of marketed drugs currently have companion diagnostics, 30% drugs in late development and 50% drugs in early development stages rely on biomarker data. Roche has projected the in vitro diagnostic market size to increase from $44bn in 2010 to $57bn in 2015, a 5% CAGR. However, the molecular diagnostic market may grow at a 9% CAGR over the same period, from $3bn to $5bn. More specifically, Qiagen estimates that the companion diagnostics market is still immature but growing at 20-25% CAGR.

Figure 139: The global in-vitro diagnostics market, 2010 and 2015E



Source: Roche

Therapeutic review

Therapeutic review

Therapeutic review (cont'd)

Introduction to cardiovascular disorders

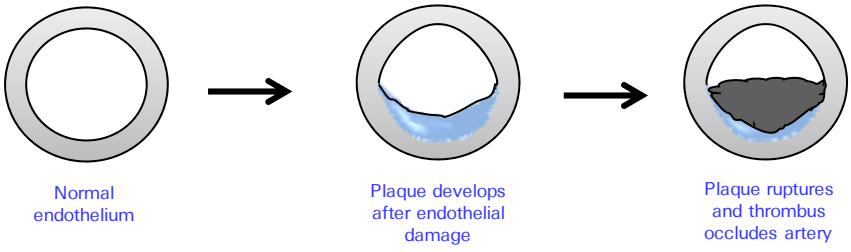
Introduction

Cardiovascular disease usually refers to a group of disorders affecting the heart and large blood vessels. It encompasses a spectrum of conditions from narrowing of the blood vessel to ischemia (insufficient blood flow) and occlusion (complete blockage). The most common complications that result are heart attacks and strokes. The World Health Organization (WHO) estimates that by the end of 2030, the global number of deaths from cardiovascular disease will rise to 23.6 million annually.

Atherosclerosis

Atherosclerosis is the narrowing of the lumen of large and medium-sized arteries due to the formation of plaques on the inner lining of the blood vessel. It evolves over many years, during which time it is clinically silent. It is thought that injury to the lining of arteries (endothelium) encourages white blood cells and low density lipoproteins (LDL cholesterol) to attach to the damaged area. Rather than being released, as is the case in healthy endothelium, the LDL cholesterol is oxidised and hardens, after which it is absorbed by specialised white blood cells called macrophages. These necrotic macrophages then migrate under the endothelium, after which the damaged area is covered by a fibrous cap of platelets, fibrin and regenerated smooth muscle. This fibrous mesh overlying a core of lipid and necrotic (dead) tissue is called a plaque. Although the plaque and narrowing in itself is usually not dangerous, if it ruptures, the exposed underlying tissue acts as a focus for a blood clot, which may potentially lead to occlusion of the artery, and death of the organ supplied by the artery. This sudden occlusion of blood flow is the cause of heart attacks and strokes (occlusion of blood to the brain). Numerous risk factors in this process exist, including cigarette smoking, hypertension, obesity, and high levels of certain cholesterols (namely LDL cholesterol) in the blood. In addition, some families exhibit a genetic predisposition to developing atherosclerosis.

Figure 140: Stages in atherosclerosis



Source: Deutsche Bank

Clearly, several steps in the atherogenic process are potential targets for pharmacological attack, not least the synthesis and breakdown of LDL cholesterol. Equally, the role of hypertension (high blood pressure) as a potential cause of initial endothelial damage makes it an important area for pharmacological intervention. Both of these strategies are discussed over the following pages.

Hyperlipidaemia

- Worldwide sales of cholesterol-lowering drugs in 2011 totalled c.$30bn.
- Class leaders in 2011 were Pfizer's Lipitor, AstraZeneca's Crestor, and Merck's Zetia and Vytorin.

Hyperlipidaemia refers to a condition of abnormally raised level of lipids (fat) in the blood. This fat can take the form of triglycerides (three fatty acids attached to a glycerol molecule), phospholipids or cholesterol, the most important of which in heart disease is cholesterol. The World Health Organization (WHO) estimates that high levels of cholesterol may be responsible for 60% of heart disease and 40% of strokes. In North America, c.35% of adults over the age of 40 have elevated levels of total cholesterol.

Physiology

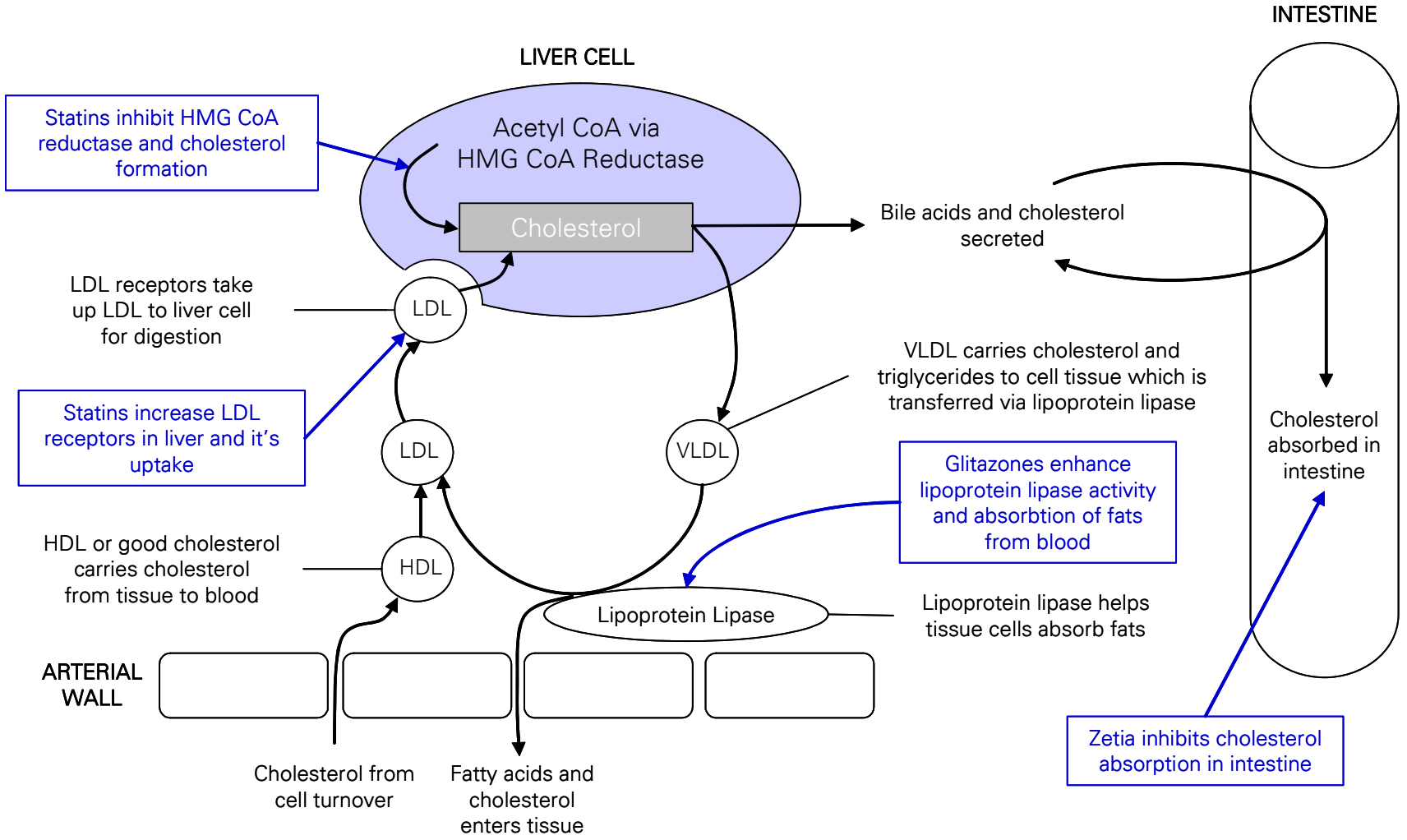
Cholesterol is vital for normal body function. It is a core component of cell membranes and is the key building block for many hormones produced by the body. It also forms an important part of the bile acids that are secreted by the liver into the gastrointestinal tract to aid digestion. Around 80% of the cholesterol needed each day is produced by the body, and the rate-limiting step in its production in the liver is the enzyme HMG-CoA reductase (3-hydroxy 3-methylglutaryl-CoA).

Because cholesterol is not soluble in blood, it is transported in a complex called a lipoprotein. As well as cholesterol, lipoproteins consist of triglycerides, phospholipids and proteins called apolipoproteins. There are several different classes of lipoproteins, each of which plays a different role and which are differentiated from each other by size, density and the relative proportions of core lipids that they carry. Key among these are very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). The function of each is as follows:

- **VLDL** - These lipoprotein complexes carry triglycerides (fats) and cholesterol from the liver to the rest of the body, wherein triglycerides are removed and absorbed into tissue cells with the help of an enzyme called lipoprotein lipase. Triglycerides provide a source of energy.
- **LDL** - After VLDL loses its triglyceride, it becomes cholesterol rich and is called LDL. Some LDL cholesterol is also taken up by the tissues. Most, however, return to the liver, where they are absorbed via specific LDL receptors.
- **HDL** - This lipoprotein absorbs cholesterol which is released from cell breakdown in tissues and carries it back to the liver, or exchanges it with VLDL so that HDL is regenerated, and VLDL is converted into LDL. This latter process is mediated by the enzyme cholesteryl-ester transfer protein (CETP).

It is the cholesterol-rich LDL which is the key protagonist of atherosclerosis, hence, its title of 'bad cholesterol.' By contrast, as a carrier of cholesterol away from tissue, HDL cholesterol is often referred to as 'good cholesterol.' Clinical studies have shown that a 1% increase in LDL cholesterol levels is associated with a 2% increase in the risk of coronary heart disease. In patients without coronary heart disease, desirable levels of total cholesterol are stated as being under 200mg/dL, of which LDL cholesterol should be under 130mg/dL. Figure 141 describes the cholesterol cycle and drug mechanisms.

Figure 141: The statins inhibit HMG-CoA reductase



Source: Rang, Dale & Ritter, Deutsche Bank

Pharmacological treatment

Statins

Several drugs are used to treat raised levels of cholesterol. Of these, by far the largest and most important class is the statins. Introduced in 1987, the statin class today is responsible for annual sales of over $20bn globally but is likely to decline in the next few years with the recent patent expiry of its leading drug, Lipitor. The class is generally well tolerated, with mild and infrequent side effects, such as stomach upset, insomnia and rash. Rarer but important side effects include muscle breakdown (rhabdomyolysis) and liver enzyme abnormalities.

The statins have a two-fold effect on cholesterol, each of which is illustrated in Figure 141. First, they are potent inhibitors of HMG-CoA reductase and so limit the production of cholesterol in the liver. Second, by reducing internal production of cholesterol, statins stimulate the synthesis of LDL receptors in the liver, which increases absorption of LDL out of blood plasma into the liver.

Today, there are several statins available on the market. The class leader in 2011 was Pfizer's Lipitor (atorvastatin), which, at its maximum dose of 80mg, has been shown to reduce the level of LDL cholesterol in the plasma by around 60%. Lipitor sales have declined since its patent expired in November 2011. Since its launch in 1997, Lipitor became the world's first $10bn drug in 2004, but sales declined in recent years as other statins offered competition and cheap generic versions of statins (e.g., Zocor) have entered the market.

The best-in-class statin, AstraZeneca's Crestor, saw a boost in its sales in 2008 with the JUPITER study results. The trial demonstrated that Crestor decreases cardiovascular morbidity and mortality in high risk patients (with elevated CRP levels), even if they did not have elevated LDL. However, the SATURN study results in 2011 failed to show a significant reduction in coronary artery plaque volume for Crestor versus Lipitor, though reduction in total atheroma volume was significantly higher in the Crestor arm.

Figure 142: Comparison of cholesterol-lowering properties of leading statins

Product (max dose)	Total cholesterol	LDL	HDL	Triglycerides
Lipitor (80mg)	-45%	-60%	5%	-37%
Zocor (80 mg)	-31%	-36%	16%	-33%
Pravachol (80 mg)	-27%	-37%	3%	-19%
Lescol (80 mg)	-27%	-36%	6%	-18%
Crestor (40 mg)	-46%	-63%	10%	-28%
Vytorin (10mg/80mg)	-43%	-60%	6%	-31%

Source: Company data

Ezetimibe

Aside from the statin class, Merck and Schering-Plough have launched Zetia (ezetimibe), the first in a family of cholesterol-lowering drugs that inhibit the absorption of cholesterol in the intestine. This distinct mechanism of action makes Zetia complementary to the statins, which work in the liver. In clinical trials, Zetia demonstrated a 25% further reduction in LDL, along with improvements in both HDL and triglyceride levels, when added to ongoing statin therapy. Given that the majority of Zetia prescriptions are used in combination with statins, Merck and Schering-Plough followed up the Zetia launch with a Zetia-Zocor fixed combination called Vytorin. This drug was positioned as a potent first-line alternative to the likes of Lipitor and Crestor. Zetia received a setback following results of the ENHANCE study, which showed that

Vytorin failed to demonstrate a significant effect on atherosclerotic plaque progression compared to Zocor (simvastatin) alone. In addition, the drug suffered was again hit when the SEAS trial in early 2008 suggested an increased risk of cancer with Vytorin. However, the FDA subsequently assessed this latter association to be unlikely. Following Lipitor patent expiry, a atorvastatin-Zetia combination is expected soon, given atorvastatin's superiority over simvastatin.

Fibrates

Fibrates are an older class of drugs which lower LDL cholesterol to a more limited extent, but which have the additional beneficial effect of reducing triclyceride levels and increasing HDL levels. As such, they are often used as a treatment for elevated triglyceride levels or as an add-on therapy to statins. However, the class has been associated with an increased (albeit small) incidence of cancer and gallstones, and may together with statins potentiate the risk of rhabdomyolysis. Fibrates work through their activation of PPAR-α (peroxisome proliferator-activated αreceptor).

Figure 143: Leading cholesterol-lowering drugs

Name	Generic	Company	2011 sales ($)
Lipitor	atorvastatin	Pfizer	$10.8bn
Crestor	rosuvastatin	AstraZeneca/Shionogi	$7.1bn
Zetia	ezetimibe	Schering-Plough/Merck	$2.7bn
Vytorin	ezetimibe/simvastatin	Schering-Plough/Merck	$1.9bn
Tricor/Trilipix	Fenofibrate/Fenofibric acid	Abbott Laboratories	$1.7bn

Source: Company data, EvaluatePharma, Deutsche Bank estimates

Clinical end-points

The key clinical end-point for the statins is their efficacy in reducing total blood cholesterol over a defined period (typically eight weeks). Within this, data should measure the reduction in LDL-C, increases in HDL-C and reduction in triglycerides. Longer-term effects on cardiovascular events in at-risk patients are also key outcome measures for longer-term clinical trials.

Pipeline products

With Lipitor, Crestor and Vytorin already offering potent (>60%) LDL cholesterol lowering, most attention has turned to drugs that more specifically target other lipid markers or address other underlying contributors to atherosclerosis such as inflammation.

HDL-C increasing drugs

The current focus has been on drugs which inhibit the cholesteryl ester transfer protein (CETP), responsible for transferring cholesterol away from good HDL-C to apoB containing lipoproteins (including LDL and VLDL). Thus, CETP activity decreases HDL cholesterol and reduces its beneficial effects, which involve transporting cholesterol from tissues to the liver. In addition, it increases the cholesterol content of very-low-density lipoprotein (vLDL) and LDL. Inhibition of CETP could increase HDL-C levels, making it an attractive therapeutic target.

The first drug in this class, Pfizer's Torcetrapib was suspended amidst data in Phase III studies which showed an association with higher blood pressure. This was attributed to an associated increase in aldosterone and is not thought to be a class-wide effect. Roche's dalcetrapib is different in mechanism of action, as it specifically modulates

CETP, while Torcetrapib binds the CETP-HDL complex. However, dalcetrapib also failed to show efficacy in Phase III trials and development was terminated in March 2012. Merck's anacetrapib and Eli Lilly's evacetrapib differ from their predecessors in mechanism and efficiency, and remain high-risk but potentially high-reward pipeline projects.

Inflammation

Atherosclerosis is now believed to be not just the result of elevated blood lipids, but also a consequence of chronic inflammation. This inflammation plays a critical role in plaque initiation and progression. This hypothesis is supported by evidence that elevated levels of biomarkers, including C-reactive protein (CRP), are associated with increased risk of cardiovascular events. In addition, patients with inflammatory disorders including RA, Lupus, psoriasis and gout have an increased risk of heart attack. Drugs in development that target inflammation include GlaxoSmithKline's darapladib, a liproprotein-associated phospholipase A2 (Lp-PLA2) inhibitor in Phase III trials and Novartis' Ilaris (an antibody that blocks the inflammatory cytokine IL-1beta).

Improved LDL-C lowering drugs

Although statin therapy is highly effective for most patients, some cannot tolerate or obtain goal LDL-C targets using existing drugs. A number of companies are developing new LDL-C lowering agents in patients with genetic abnormalities that lead to increased LDL-C and early cardiovascular disease such as familial hypercholesterolemia and in patients not well controlled on existing medications. These drugs include Sanofi's Kynamro (an an antisense molecule to the Apolipoprotein B-100 gene that encodes a key component of LDL), Aegerion's lomitapide (MTP inhibitor) and drugs targeting PCSK9 (a protein involved in LDL-C receptor degradation) from Sanofi/Regeneron, Amgen, Pfizer and Roche. Most of these drugs (except Aegerion's lomitapide) require either intravenous or subcutaneous administration and are thus likely to be limited to the most severely affected patients.

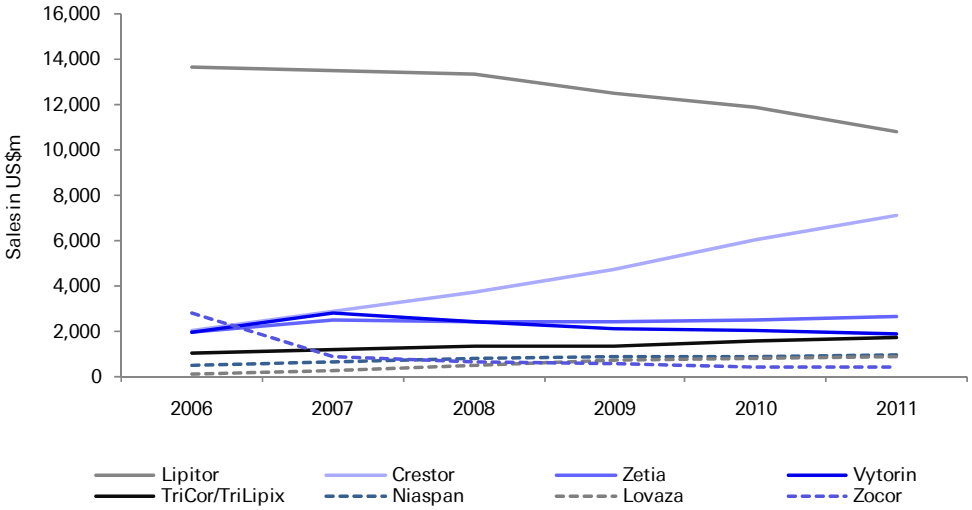
Figure 144: Pipeline drugs for dyslipidaemia

Product	Stage	Company	Class
Kynamro	Filed	Sanofi	Apolipoprotein B-100 (ApoB-100) antisense
AMR101	Filed	Amarin	Omega-3 fatty acid
Lomitapide	Filed	Aegerion Pharmaceuticals	Microsomal triglyceride transfer protein (MTP) inhibitor
Anacetrapib	Phase III	Merck & Co	CETP inhibitor
AKR-963	Phase III	Trygg Pharma	Lipid lowering agent
Epanova	Phase III	Omthera Pharmaceuticals	Omega-3 fatty acid
TAK-085	Phase III	Takeda	Omega-3 fatty acid
Nidadd	Phase III	Genovate Biotechnology	Vitamin B3
Darapladib	Phase III	GlaxoSmithKline	Lipoprotein-associated phospholipase A2 (Lp-PLA2) inhibitor
Ilaris	Phase III	Novartis	LI-1 beta blocker
JTT-302	Phase II	Japan Tobacco	CETP inhibitor
Evacetrapib	Phase II	Eli Lilly	CETP inhibitor
REGN727/SAR236553	Phase III	Sanofi/Regeneron	PCSK9
AMG145	Phase II	Amgen	PCSK9
PF-04950615	Phase II	Pfizer	PCSK9
RG7652	Phase III	Roche	PCSK9
DRL 17822	Phase II	Dr. Reddy's Laboratories	CETP inhibitor

Source: Company data, Deutsche Bank

Sales

Figure 145: Sales of leading cholesterol-lowering drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 146: Sales of leading cholesterol-lowering drugs ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Lipitor	Pfizer / Astellas	13,696	13,533	13,353	12,511	11,870	10,804
Crestor	AstraZeneca / Shionogi	2,049	2,887	3,774	4,763	6,030	7,089
Zetia	Merck	1,954	2,521	2,417	2,413	2,480	2,677
Vytorin	Merck	1,933	2,845	2,436	2,112	2,014	1,882
TriCor/TriLipix	Abbott Laboratories	1,048	1,229	1,356	1,375	1,608	1,719
Niaspan	Abbott Laboratories	524	667	786	855	927	976
Lovaza	GlaxoSmithKline	154	314	537	704	819	912
Zocor	Merck & Co	2,803	877	660	558	468	456

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Thrombosis

- World anti-thrombotic sales totalled c.$23bn in 2011.
- Lead products include Sanofi's Lovenox/enoxaparin, a low-molecular-weight heparin, and Plavix, an anti-platelet agent co-marketed with Bristol-Myers Squibb.

Thrombosis is the formation of a blood clot in veins or arteries (or vasculature) in the absence of bleeding. In the arteries, it tends to arise following the rupture of an atherosclerotic plaque, while in the veins, it is generally associated with static blood flow. Once a thrombus is established, it can block key blood vessels, including those in the heart, or it can break away forming an embolus, which may later lodge in the lungs (pulmonary embolism) or the brain (cerebral embolism), causing a stroke.

Physiology

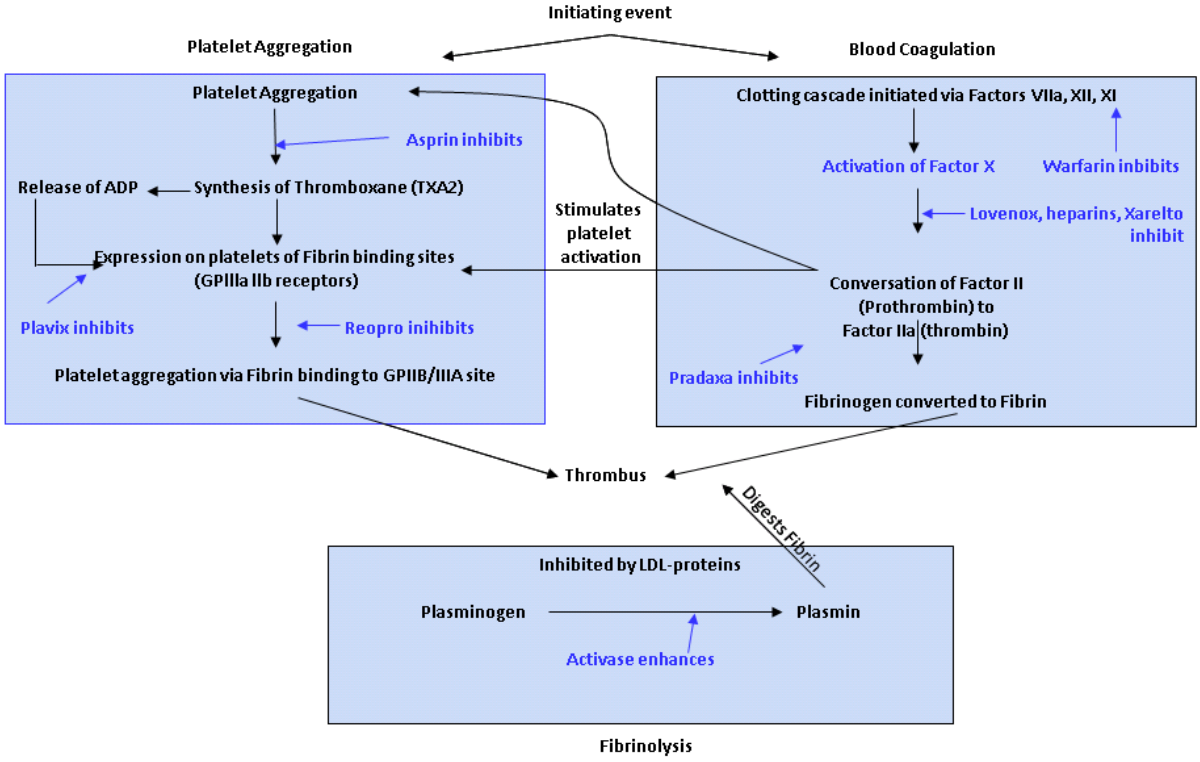
The creation of a blood clot (thrombus) involves the initiation of the blood-clotting cascade. In healthy blood vessels, the arterial lining (called the endothelium) produces proteins which keep the clotting cascade in check. However, if the lining is damaged, e.g., in a cut or a plaque rupture, these proteins are not produced and the underlying surface represents a focus upon which a thrombus can form. Key to this is the activation of platelets and a host of other blood proteins, such as fibrinogen, thrombin and other blood enzymes, or 'factors,' which travel about the body in the blood system in an inactive state. Once activated, the various factors form part of a chain reaction that results in a clot being formed.

The creation of a thrombus can simplistically be broken down into three different pathways, each of which is integral to the formation of a thrombus. A general overview of the different cascades is shown in Figure 147.

- **Platelet aggregation** – When the endothelium is damaged, it exposes proteins which activate circulating platelets in the blood. Activated platelets release substances, e.g. ADP and thromboxane A2, reinforcing a positive feedback loop of activation of other platelets. Activated platelets bind to the collagen in the vessel wall, and cross-link with fibrin (see coagulation pathway) and each other via surface glycoprotein IIb/IIIa receptors. Drugs that act to block the activation of platelets are called anti-platelet aggregation agents. Such drugs include aspirin, Sanofi's Plavix, AstraZeneca's Brilinta and Eli Lilly's Effient.
- **Coagulation pathway** – Proteins known as clotting factors normally circulate in an inactive state in the blood. Injured tissue exposes proteins which activate clotting factors, culminating in the formation of Factor X, which activates the enzyme thrombin. Thrombin is responsible for the cleaving of fibrinogen into fibrin, the main protein involved in the architecture of a blood clot. Anti-coagulants such as heparin and warfarin block different parts of the coagulation pathway, and hence interfere with formation of fibrin. Direct factor Xa inhibitors such as Bayer's Xarelto bind to the active site of factor Xa and prevent thrombin activation.
- **Fibrinolysis** – Blood contains different proteins which break down fibrin blood clots, and help clear up insoluble fibrin material that may form when they are not needed. Hence, the body is in a constant state of clot formation and

breakdown. Drugs that enhance the activity of clot dissolution include tissue-type plasminogen activators (TPAs, e.g., Genentech's Activase), which play an important part in dissolving blood clots in the acute phase of a heart attack and thromboembolic strokes.

Figure 147: Three pathways involved in the creation of a thrombus



Source: Rang, Dale & Ritter , Deutsche Bank

Though the pathway for forming a blood clot is similar, the mechanism by which they form and the consequences are different, depending on whether they occur in an artery or a vein.

Arterial blood clots

Arteries are blood vessels which carry blood away from the heart, and supply various end organs such as the heart itself (coronary arteries) and the brain (cerebral arteries). Blood clots in arteries are usually related to damage to the blood vessel lining (endothelium), e.g. atherosclerotic plaque rupture, which expose the underlying collagen. This acts as a focus for platelets to aggregate and form a platelet 'plug.' Though later, there is recruitment of the coagulation pathway and some fibrin being formed, a large part of the clot consists primarily of platelets. This clot may be large enough to occlude the artery in the first instance, or it may break off and block a smaller blood vessel further downstream. In either scenario, blockage of blood flow to the organ results in death of the organ (or the supplied portion of the organ), i.e., heart attacks and strokes.

As the pathway that predominates in arterial clots is platelet aggregation, the focus of treatment and prevention of arterial clots is on anti-platelet aggregation agents such as aspirin and Plavix (Sanofi).

Venous blood clots

Veins are blood vessels which carry blood from the organs back to the heart. Due to a variety of factors, blood tends to flow more slowly in veins compared to arteries, resulting in pooling or stasis of blood in the veins, which predisposes to the formation of a blood clot. This blood clot is comprised primarily of fibrin and red blood cells, with platelets playing a smaller role. The issue with venous blood clots is that they may break off, drift to the heart, and get lodged in the lung, blocking blood flow. This is known as pulmonary embolism (PE), and can be fatal.

One significant source of venous blood clots is the deep veins of the leg (deep venous thrombosis or DVT), as they are more vulnerable to venous stasis, e.g. as a result of immobility following orthopaedic surgery, or traveller's thrombosis (e.g., when flying economy class on long journeys with restricted movement). Another frequent source of venous clots is a mural thrombus (blood clot within the chambers of the heart), e.g., due to atrial fibrillation (a form of irregular heart rhythm) or heart valve replacement. In both these cases, there is a disruption to blood flow within the heart, resulting in areas of flow and pooling.

As the pathway which dominates in venous blood clots is the coagulation cascade, the focus of treatment and prevention is the drugs which block the formation of fibrin (anticoagulants, e.g., warfarin, Xarelto) or dissolve clots (fibrinolytics, e.g., Activase).

Pharmacological treatment

As we have discussed, depending on the location of the thrombus, different classes of agents have been developed to treat the thrombus.

Figure 148: Summary of anti-thrombotic agents

Broad class	Platelet anti-aggregation agents	Warfarin	Heparins	Fibrinolytics	Clotting Factor Inhibitors
Sales in 2011 ($)	$13.3bn	$0.3bn	$5.2bn	$0.8bn	$1.9bn
Pathway	Inhibit activation of platelets	Vitamin K reductase inhibitor	Inhibit activation of blood factors	Encourage creation of plasmin	Inhibit the activation of thrombin
Key Products	Plavix, Aspirin, ReoPro	Coumadin	Lovenox, Arixtra, Fraxiparine	Activase, Retavase	Pradaxa, Xarelto, Eliquis
Administration	Oral/injectable	Oral	Injection	Injection	Oral
Adverse effects	Rash, diarrhoea, haemorrhage	Haemorrhage	Haemorrhage, cytopaenia	Haemorrhage	Haemorrhage

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Platelet anti-aggregation agents

Anti-aggregation agents are the only class used in the treatment and prevention of arterial clots, principally in atherosclerosis and following heart attacks and strokes. They work at different stages of the pathway that leads to the aggregation of platelets, and clumping of platelets with fibrin. Several are taken orally and can be used as prophylactics (for prevention), reducing the risk of thrombosis and coronary events (aspirin is probably the best known example). The newest addition to the category is AstraZeneca's Brilinta, which works through a similar mechanism to Plavix, by blocking ADP receptors on platelets, but via a reversible mechanism. It offers the advantage of having a faster onset and a more pronounced platelet inhibition.

Figure 149: Platelet anti-aggregation agents

Brand name	Generic name	Company	Sales 2011 ($)
Plavix	clopidogrel	Bristol-Myers Squibb / Sanofi	$9.7bn
Pletal	cilostazol	Otsuka Pharmaceutical	$0.6bn
Aspirin Cardio	aspirin	Bayer	$0.6bn
Aggrenox/Asasantin	aspirin & dipyridamole	Boehringer Ingelheim	$0.5bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Warfarin

Warfarin is the most commonly used anti-coagulation agent for venous clots. Discovered in the 1920s and originally used as rat poison, the product has been generic for many years. Warfarin acts by inhibiting the reduction of a key component in the clotting process, vitamin K (K for Koagulations vitamin in German), into a reduced form which is key to the production of certain clotting factors (Factors II, VII, IX and X). However, the therapeutic use of warfarin requires careful titration to achieve a balance between giving too much (risk of bleeding) or too little (coagulation remains unaffected). Use is further complicated by the time taken for the drug to become active (two days) and because of numerous drug-drug interactions that alter its activity. The effect of warfarin is monitored by measuring the time taken to create Factor II (prothrombin) and is expressed as an International Normalised Ratio (INR). Dosage is usually adjusted to give an INR of 2.0-3.0 depending on the clinical situation (occasionally 2.5-3.5 or up to 4.0). Given the inconvenience of frequent blood tests and uncertainty in titration, there is a large potential demand for a drug with a more predictable profile. Pharmaceutical companies have recognised this, and are in the process of developing drugs which seek to replace warfarin (e.g., clotting factor inhibitors, see later).

Heparins

One of the oldest classes of drugs for venous clots, heparins block the action of the enzyme, thrombin, and through that the coagulation pathway. However, traditional heparin, which is derived from natural sources (pig intestinal mucosa), contains a mixture of different molecular weights, resulting in an unpredictable pharmacological profile. It is given by infusion, and blood tests are required to ensure that a therapeutic dose is achieved. Low molecular weight heparins (LMWH) are increasingly used, as they are produced from isolates of a more consistent molecular weight, resulting in a more predictable pharmacological profile. They can be administered by injection once a day and do not require a blood test to ensure efficacy.

Figure 150: Heparins

Brand name	Generic name	Company	Sales 2011
Lovenox/enoxaparin	enoxaparin sodium	Sanofi/Novartis	$4.0bn
Arixtra	fondaparinux sodium	GlaxoSmithKline	$0.5bn
Fragmin	dalteparin sodium	Pfizer/Eisai	$0.6bn
Fraxiparine	nadroparin calcium	GlaxoSmithKline	$0.4bn
Heparin Sodium	heparin sodium	Generic	$0.3bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Fibrinolytics

The smallest class of anti-thrombotic drugs, fibrinolytics, is the only class that actively breaks down clots, versus merely blocking new clot formation. Though they work principally on fibrin, they are used in arterial clots as well. They are typically administered within a few hours following the onset of symptoms in heart attacks, thromboembolic strokes and pulmonary embolism to dissolve clots and restore blood flow to the organ. However, by actively dissolving all blood clots, their main drawback

is a high incidence of severe bleeding and gastric haemorrhage. The largest drugs in the class are Roche & Boehringer's Alteplase.

Figure 151: Fibrinolytics

Name	Generic	Company	Sales 2011 ($)
Activase/Actilyse	alteplase	Roche/Boehringer Ingelheim	$0.8bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Clotting factor inhibitors

The newest class of drugs used to treat venous thrombosis targets the clotting factors which produce fibrin. Currently, Pradaxa (Factor II inhibitor from Boehringer Ingelheim), Xarelto and Eliquis (Factor Xa inhibitors from Bayer and Pfizer/BMS, respectively) are oral clotting factor inhibitors which have been approved or are pending approval (the FDA issued a CRL for Eliquis in June 2012, for the prevention of stroke and systemic embolism in atrial fibrillation, requesting additional data). Clotting factor inhibitors are used for stroke prevention in atrial fibrillation, prevention of venous thromboembolism following knee or hip surgery, preventing blood clots in other conditions such as DVT and potentially in acute coronary syndrome (ACS). Other candidates in this class include otamixaban (Factor Xa inhibitor fom Sanofi) and edoxaban (Factor Xa inhibitor from Daiichi Sankyo), which are also in late-stage clinical trials.

Clinical end-points

The key end-points used to assess the performance of anti-thrombotic agents are the reduction in the incidence of clotting or thrombo-embolic events compared to placebo. In addition, bleeding is a key limiting side effect, and anti-thrombotic agents should not significantly increase the risk of (potentially) uncontrollable bleeding. Given the high profile failure of AstraZeneca's Exanta, regulatory authorities also have an increased focus on liver enzyme abnormalities for new antithrombotic drugs.

Pipeline products

Apixaban, edoxaban and otamixaban are anticoagulants currently being investigated in late-stage trials in a variety of indications such as atrial fibrillation and DVT. In the anti-platelet field, AstraZeneca launched Brilinta for ACS in 2011, which offers the advantage of having a faster onset and a more pronounced platelet inhibition versus Plavix. It demonstrated better efficacy than Plavix in acute heart attacks in late-stage trials and reduced cardiovascular deaths.

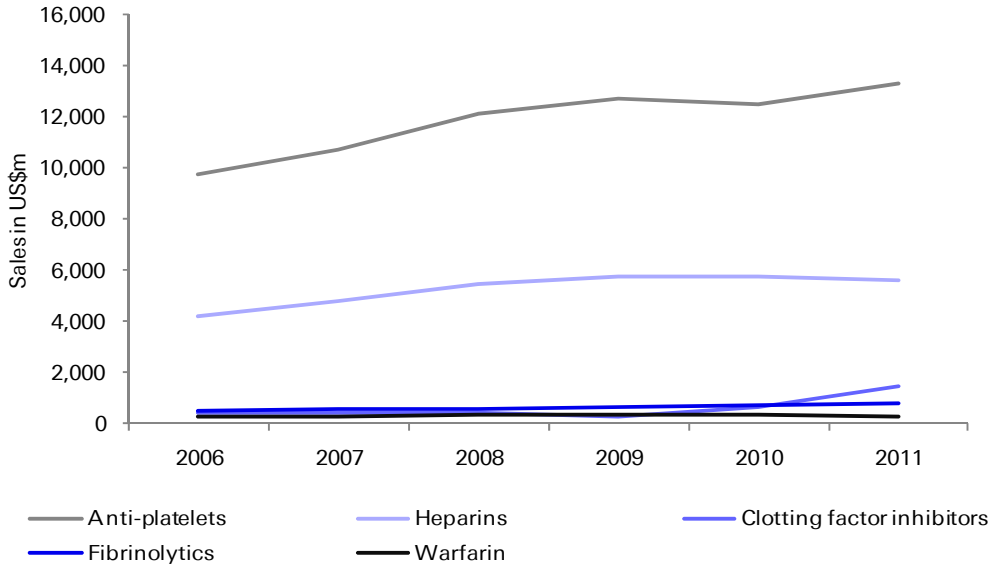
Figure 152: Selected pipeline anti-thrombotics

Name	Company	Mechanism	Status
Visamerin	Sanofi	Indirect Factor Xa / IIa inhibitor	Filed
Eliquis (Apixaban)	Pfizer/BMS	Factor Xa inhibitor	Phase III
Edoaban	Daiichi Sankyo	Factor Xa inhibitor	Phase III
Otamixaban	Sanofi	Factor Xa inhibitor	Phase III
Voraxapar	Merck & Co	PAR1 thrombin receptor antagonist	Phase III
Desmoteplase	Lundbeck	Plasminogen activator	Phase III
THR-100	ThromboGenics	Plasminogen activator	Phase III
M118 (adomiparin)	Momenta Pharmaceuticals	Indirect Factor Xa / IIa inhibitor	Phase II
AZD0837	AstraZeneca	Direct Thrombin inhibitor	Phase II
DB-772d (staphylokinase)	Daiichi Sankyo	Factor Xa inhibitor	Phase I
SAR126119	Sanofi	TAFIa inhibitor	Phase I
AZD6482	AstraZeneca	PI3Kbeta inhibitor	Phase I

Source: Company data, Deutsche Bank, EvaluatePharma

Sales

Figure 153: Sales of anti-thrombotic drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 154: Sales of anti-thrombotic drugs ($ m)

Class	2006	2007	2008	2009	2010	2011
Anti-platelets	9,787	10,735	12,143	12,702	12,488	13,350
Heparins	4,229	4,829	5,465	5,764	5,789	5,637
Clotting factor inhibitors	469	418	414	295	634	1,496
Fibrinolytics	542	583	595	691	713	806
Warfarin	280	283	338	356	351	324

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Hypertension

- Worldwide sales of anti-hypertensives in 2011 totalled c.$37bn.
- Key classes include angiotensin II inhibitors (ARBs) and calcium antagonists, as well as older drugs such as beta blockers and ACE inhibitors.
- Upcoming pressure with patent expiries in key ARBs class
- Market largely dominated by generics. Lead branded product is Diovan (Novartis).

Hypertension, or high blood pressure, is a common disorder where there is increased pressure in the blood vessels in the body. It is largely asymptomatic, but is clinically important because it is associated with increased risks of heart attacks, strokes and renal failure if not effectively treated. Until the 1950s, there was no effective treatment. However, today there are several classes of drug that can be used to treat the disease effectively. Hypertension affects more than one in four North American adults. In 90-95% of cases, the cause of the increase in blood pressure is not known, although 60% of affected individuals are overweight. The condition remains undiagnosed in more than 20% of these people, though this number is possibly higher in communities where there are no routine blood pressure screenings.

Physiology

Blood pressure in the arteries is generated by the interplay between blood flow and resistance to blood flow. It reaches a peak during the pumping of the heart (cardiac systole) and a trough at the end of the heart's period of relaxation (diastole). In effect, it can be defined as the product of cardiac output (CO) and the total peripheral resistance (TPR) offered by the blood or vascular system. Cardiac output, which is a function of heart rate and stroke volume (defined as volume of blood pumped out of the heart per heartbeat), is the major determinant of systolic pressure, while peripheral resistance largely determines diastolic pressure. As such, treatment is typically directed at altering these variables.

Arterial blood pressure is measured in millimetres of mercury and recorded as systolic pressure over diastolic. The Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure has defined hypertension as having a systolic blood pressure or SBP (blood pressure during the contraction phase of the heartbeat) of 140mm Hg or above, or a level of diastolic blood pressure or DBP (pressure during the resting stage of the heart) of 90mm Hg or above. This compares with normal blood pressure of 120mm Hg or below for SBP and 80mm Hg or below for DBP.

Several biological systems control blood pressure and a sophisticated feedback system exists. Key regulatory mechanisms, each of which is mentioned below, include the actions of the nervous system, hormones, control of body fluid and regulators produced by the blood vessels themselves.

- **Nervous system**: One of the key mechanisms for maintaining blood pressure is through the actions of the nervous system. Noradrenalin, a chemical messenger, is released by nerve endings located on blood vessels (including those of the heart) and acts on alpha and beta receptors. Stimulation of alpha

receptors on blood vessels serves to narrow the vessels (called vasoconstriction), thereby increasing peripheral resistance and consequently, blood pressure. Equally, stimulation of beta receptors in the heart ('beta 1' receptors) results in an increase in contractility and heart rate, thereby also increasing blood pressure (most beta blockers act on the beta 1 receptor). Countering this, a system of pressure sensors (or baroreceptors) located at the nerve endings that attach to large arteries (including those of the heart) provide feedback to the brain, and hence the central nervous system, so regulating the rate of noradrenalin release.

- **Hormones**: Renin is an enzyme secreted by the kidney in response to low circulating blood volume. It acts to convert a protein called angiotensinogen into angiotensin I. Angiotensin I is then converted into angiotensin II by another enzyme called the Angiotensin-converting Enzyme (ACE). Angiotensin II is responsible for the majority of the effects on blood pressure, such as increasing vascular tone (reducing the width of blood vessels increases blood pressure) and increasing absorption of salt and water through other intermediaries to increase circulating blood volume. ACE inhibitors and ARBs function by blocking different points along this chain of events.
- **Vascular regulators**: The lining of blood vessels also has an important part to play in hypertension. Among other actions, endothelial cells produce nitric oxide, which acts as a vasodilator (widens the blood vessel). Muscle in blood vessel walls contains calcium channels, which regulate the concentration of calcium in the muscle and hence vaso-constriction/dilation (calcium ions stimulate muscle activity). Calcium channel antagonists act on these calcium channels in blood vessel walls and the heart.
- **Control of body fluid**: Blood pressure can also be controlled by reducing the total amount of fluid in the blood vessels. Regulated by the kidneys, water retention is influenced by the concentration of sodium (or salt) in the blood. Diuretics act to increase the excretion of water and reduce blood pressure.

Pharmacological treatment

A large number of drugs are used to treat hypertension. The market, however, is dominated by four main classes. These are the beta-blockers, calcium antagonists, ACE inhibitors and angiotensin receptor blockers (ARBs). Although each of these classes can be used alone as a monotherapy, combination regimens are usually required to achieve adequate control. Each of these key classes is described in the figures below.

Figure 155: Summarised features of the leading classes of hypertensive agents

Class	ARBs	ACE inhibitors	Ca2+ antagonists	Beta blockers
Sales 2011 ($)	$20bn	$3bn	$5bn	$4bn
Lead Product	Diovan	Coversyl	Norvasc	Toprol XL
Main Action on	Vascular	Vascular	Vascular/Heart	Heart
Side effects	Swelling	Cough, swelling	Swelling	CHF, bradycardia

Source: Company data, Deutsche Bank estimates, EvaluatePahrma

Beta blockers

The discovery of beta blockers in the 1960s represented a major breakthrough in cardiac therapy. The oldest of these four classes, it is made up largely by generic drugs. Beta blockers act mainly by inhibiting the stimulation of beta adrenergic receptors in the heart, thereby slowing the rate and strength of contraction. This reduces cardiac output and blood pressure. All branded drugs have lost patent protection, but

AstraZeneca's Toprol XL continued to enjoy strong sales in 2011 after generic versions of the drug were withdrawn as a result of quality issues.

Calcium antagonists

Calcium is vital for muscle contraction. An increase in the concentration of calcium within muscle cells precipitates their contraction. In essence, calcium antagonists work by preventing the inflow of calcium through calcium channels in heart and vascular tissue. This reduces both the strength of the heart's contraction and vascular constriction. As such, the product can also be used for angina. Patent expiry on most key products, not least Norvasc, Adalat, Cardizem and Procardia, has led to declining in class sales.

Diuretics

A diuretic is a drug which increases the amount of urine produced by the body. In the treatment of hypertension, the class of diuretics specifically used is thiazide diuretics, which increase the amount of urine produced, thereby reducing the pressure of blood filling the heart. They also have an effect through a separate pathway where they relax peripheral blood vessels, together reducing blood pressure.

Angiotensin-converting enzyme (ACE) inhibitors

ACE inhibitors were the earliest class of drugs to act on the renin-angiotensin system to control blood pressure. They exert their effect by preventing the formation of angiotensin II, a powerful vasoconstrictor. Patents of leading compounds (Coversyl, Vasotec and Zestril) have expired in the past few years, causing class dollar value sales to fall significantly.

Angiotensin II receptor antagonists (ARBs)

Angiotensin II receptor inhibitors also act on the renin-angiotensin system but do not cause the dry cough that has proved to be the limiting side effect of the ACE inhibitor class. This class too may have its best years behind it, as patents for leading drugs such as Diovan and Atacand/Blopress expire in 2012. Cozaar was the first in this class to lose patent protection in April 2010.

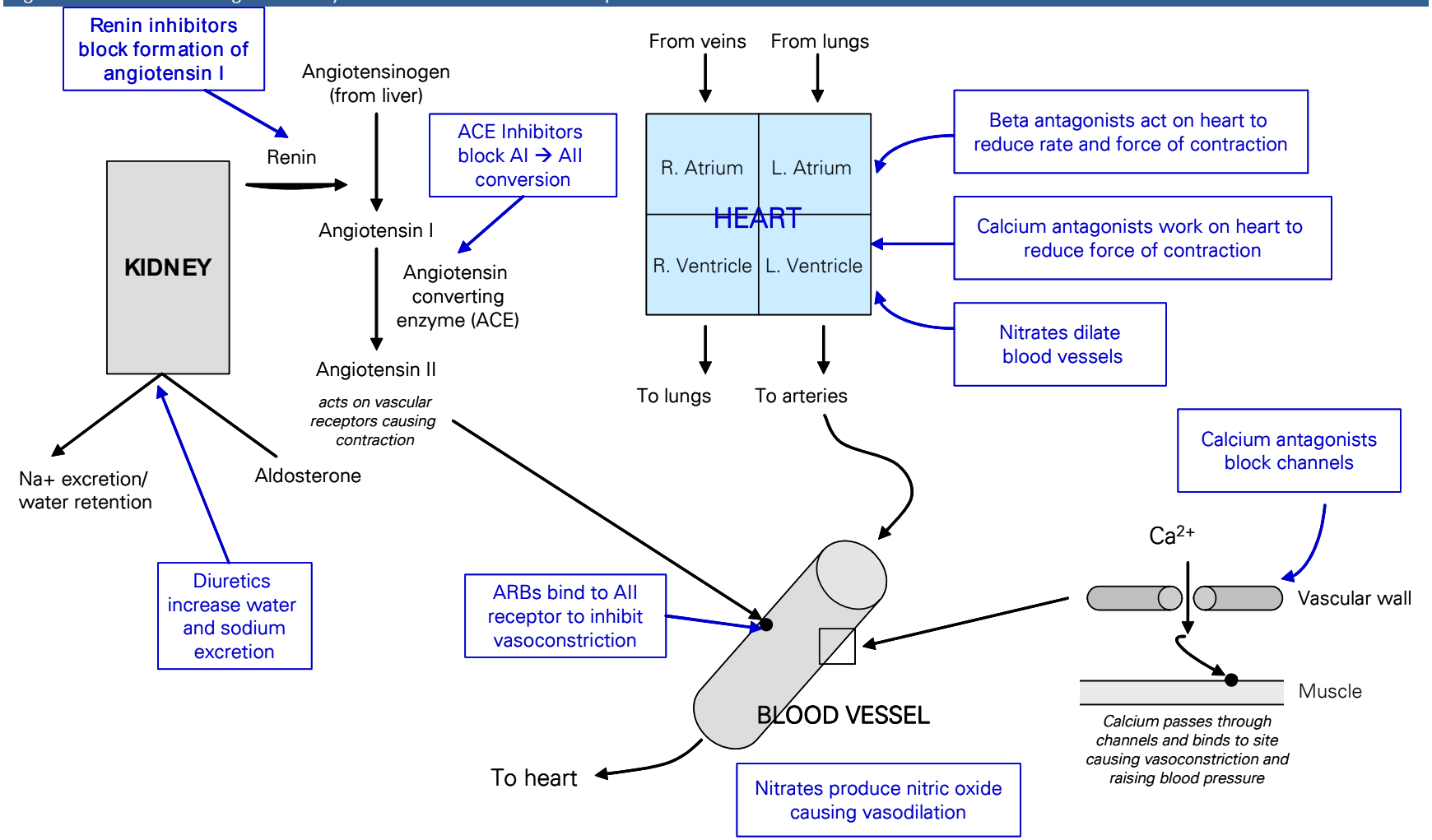
Direct renin inhibitors

The newest class of hypertensive treatments, renin inhibitors, acts on the renin-angiotensin system by inhibiting renin directly. One theoretical issue faced by ARBs is that of a feedback loop, in which more angiotensin I is produced in response to low angiotensin II stimulation. Direct renin inhibitors block the renin-angiotensin pathway further up the chain, thereby preventing the build-up of angiotensin I. Novartis' Tekturna is the sole drug on the market in this class, but its usage is set to decline following safety concerns for the drug.

Combination products

Patients with poorly controlled hypertension are frequently prescribed multiple drugs. Drugs in different classes may work synergistically, and hence are preferred in combination therapies, e.g. diuretic and ACE-inhibitors/ARBs. To facilitate compliance, combination pills have been produced which contain two or even three drugs in a single pill. This trend was driven primarily by the ARB producers, which initially bundled ARBs with a diuretic, though calcium channel blockers (Novartis' Exforge/Exforge HCT and Daiichi Sankyo's Azor) have gained market share more recently.

Figure 156: The renin-angiotensin system and its effect on blood pressure



Source: Deutsche Bank

Clinical end-points

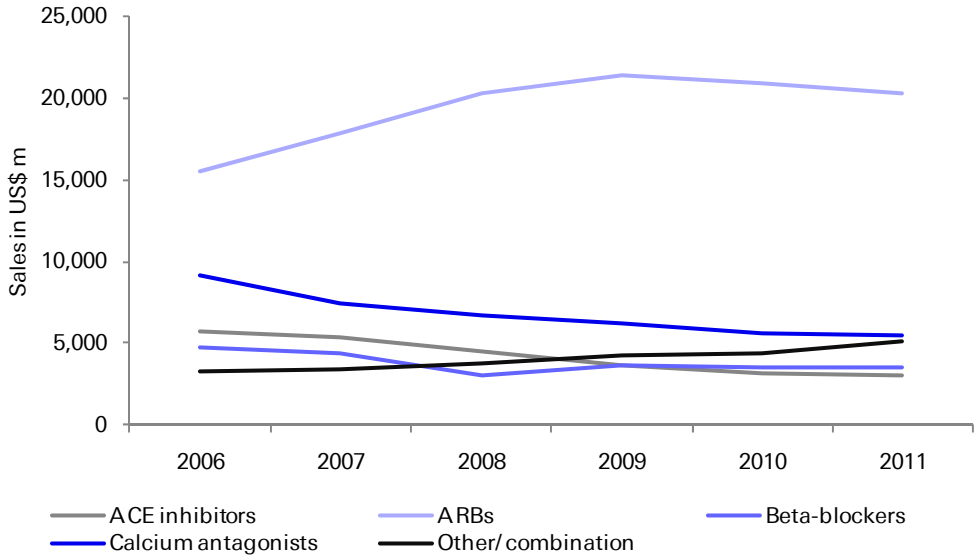
The key clinical end-points for hypertension drugs are their impact on both systolic (upper) and diastolic (lower) blood pressure. Target blood pressure levels, as dictated by international recommendations for the treatment of hypertension, are <140/90mm Hg for the majority of hypertensive patients and <130/80mm Hg for patients with diabetes or evidence of proteinuria and renal disease. Since the objective of therapy is to lower blood pressure, the greater the reduction, the more effective and interesting the product. Side effects must, of course, also be considered.

Pipeline products

Even though roughly 70% of hypertension patients do not reach their target blood pressure levels, there has been limited advance in this field since the introduction of the ARBs in the mid-1990s, bar Novartis' direct renin inhibitor, Tekturna.

Sales

Figure 157: Sales of hypertension drugs



Source: Company data, Deutsche Bank estimates, EvauatePharma

Figure 158: Sales of hypertension drugs ($ m)

Class	2006	2007	2008	2009	2010	2011
ACE inhibitors	5,777	5,368	4,493	3,620	3,153	2,975
ARBs	15,448	17,825	20,310	21,319	20,839	20,220
Beta-blockers	4,737	4,403	3,037	3,698	3,579	3,555
Calcium antagonists	9,177	7,427	6,733	6,254	5,623	5,454
Other/combination	3,239	3,364	3,830	4,300	4,423	5,067

Source: Company data, Deutsche Bank estimates, EvauatePharma

Pulmonary arterial hypertension

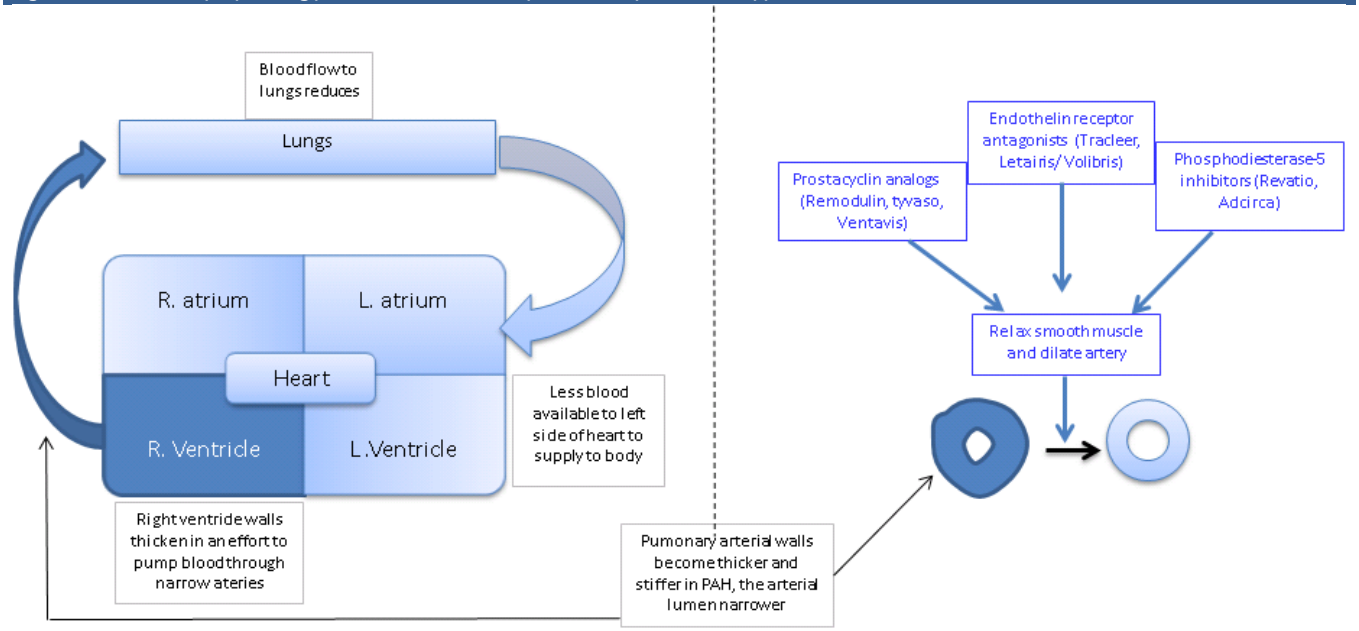
- Worldwide sales of PAH drugs in 2011 totalled c.$3.6bn.
- Estimates suggest there may be 100-200,000 patients with PAH worldwide.
- Untreated disease has a poor prognosis with 2-3 years median survival

Pulmonary arterial hypertension (PAH) is a form of high blood pressure in the arteries that lead to the lungs. This results in progressive loss of exercise capacity, places strain on the heart, ultimately leading to heart failure and death. The disease usually presents in people in their 30s and 40s, and is twice as common in females as in males. Only around 1/3rd of PAH patients are currently treated. This disparity reflects that a large proportion of patients remain undiagnosed, particularly those with co-morbid conditions.

Physiology

Pulmonary arterial hypertension is characterized by an increase in pressure in the pulmonary arterial system (which carries blood from the heart to the lungs for purification). PAH can occur on its own, where it is known as primary or idiopathic (i.e. of no known cause) or secondary to other diseases such as scleroderma, HIV, Lupus, sickle cell disease and congenital heart failure. In PAH, muscle cells in the arterial walls lose their ability to regulate death of old cells as new muscle cells are generated. The walls become thicker as cells increase in number, and the arteries narrower, making it difficult for the heart (right ventricle) to pump blood to the lungs. There may be accompanying inflammation and blood clot formation in the arteries with development of localised thickening. Over time, walls of the right ventricle become thicker as the heart attempts to pump blood through the stiffened and narrow arterial system. Exercise tolerance reduces and fatigue develops, as the left side of the heart does not receive adequate oxygenated blood from the lungs to distribute to the rest of the body. If untreated, eventual death may often occur through failure of the right ventricle.

Figure 159: Pathophysiology and treatment of pulmonary arterial hypertension



Source: Deutsche Bank

Pharmacological treatment

PAH is associated with poor prognosis and high mortality if untreated; new treatment paradigms over the past 15 years have significantly improved the prognosis. A 2010 study concluded that 5-year survival has improved to 66% versus 32% before the advent of the seven drugs discussed below. Besides diuretics and oxygen that may provide symptomatic relief, most PAH therapies are targeted at preventing the constriction and thickening of arterial wall muscles. For patients that do not respond to drugs, lung transplant is the only alternative treatment.

Calcium channel blockers

High doses of calcium channel blockers may be useful in initial treatment of PAH. However, not all patients respond to this class of drugs and fewer than 20% benefit with long term treatment. As such, the FDA also does not recommend calcium channel blockers for PAH.

Prostacyclin analogs

Prostacyclins are the most efficacious therapy for PAH and may even be effective in patients that fail other drugs. They cause vasodilatation, prevent muscle growth in the arterial wall, improve cardiac function and also inhibit clot formation. GSK's Flolan (epoprostenol) is administered as a chronic infusion through a central venous catheter; it is unstable at room temperature and is thus inconvenient for long-term use. United Therapeutics' prostacyclin analogue Remodulin (treprostinil) can be given by intravenous or subcutaneous injections, though the latter is associated with significant pain. Actelion introduced a thermostable formulation of epoprostenol (Veletri) in 2008.

Other formulations have been devised to counter the inconvenience associated with long-term intravenous infusion. The FDA approved Actelion's inhaled iloprost (Ventavis) in 2004; this method of delivery eliminates the discomfort of injections but has to be inhaled 6 to 9 times per day. Tyvaso (inhaled treprostinil), approved in 2009, has the additional advantage of 4 times daily inhalation.

Figure 160: Prostacyclin analogue therapies for PAH

Name	Company	Generic	Route	2011 sales ($)
Remodulin	United Therapeutics	treprostinil	iv/subcut	$0.4bn
Tyvaso	United Therapeutics	treprostinil	inhaled	$0.2bn
Ventavis	Actelion	iloprost	inhaled	$0.1bn
Veletri	Actelion	epoprostenol sodium	iv	<$0.1bn

Source: Deutsche Bank, EvaluatePharma, Company data

Endothelin receptor antagonists (ETRA)

Actelion's Tracleer (bosentan) and GSK/Gilead's Volibris/Letairis (ambrisentan) are the ETRA drugs currently approved for PAH. They act by inhibiting endothelin, a powerful vasoconstrictor produced in the cardiovascular system. Tracleer is a dual endothelin receptor antagonist and was first approved in 2001. Letairis, approved in 2007, selectively inhibits endothelin A and is marketed as Volibris outside the US. It is yet unclear whether selectivity is associated with a clear therapeutic benefit. Pfizer's Thelin (sitaxentan), also a selective endothelin A blocker, was approved in EU in 2006, but was subsequently withdrawn in 2011 due to hepatotoxicity.

Figure 161: ETRA therapies for PAH

Name	Company	Generic	2011 sales ($)
Tracleer	Actelion	bosentan	$1.7bn
Letairis	Gilead Sciences	ambrisentan	$0.3bn
Volibris	GlaxoSmithKline	ambrisentan	$0.2bn

Source: Deutsche Bank, EvaluatePharma, Company data

Phosphodiesterase 5 inhibitors

This category includes Pfizer's Revatio (sildenafil) and EliLilly/United Therapeutics' Adcirca (taldafil). PDE-5 inhibitors act via the nitric oxide pathway and prevent the destruction of cGMP, a substance that relaxes arterial muscle walls and prevents muscle proliferation. They PDE-5 inhibitors are also being studied for use in combination with ETRAs.

Figure 162: PDE-5 inhibitors for PAH

Name	Company	Generic	2011 sales ($)
Revatio	Pfizer	sildenafil	$0.5bn
Adcirca	Eli Lilly/ United Therapeutics	tadalafil	$0.1bn

Source: Deutsche Bank, EvaluatePharma, Company data

Clinical end-points

The majority of trials of PAH drugs have employed the 6-minute walking distance (6MWD) as a measure of efficacy. It is simply the change in distance an individual can walk on a flat, hard surface over 6 minutes, measured before the therapy is given, and then at pre-decided intervals. A patients 6MWD capacity is correlated to expected survival. However, 6MWD change is now known to be a relatively poor surrogate for clinical benefit. Trials of PAH drugs generally also assess impact on a composite measure of clinical events known as "clinical worsening" or "mortality/morbidity". Actelion's SERAPHIN trial of macitentan has recently reported the first positive results from a large long-term study using such an endpoint as the primary outcome.

Percentage change in pulmonary vascular resistance is also used as a measure of efficacy; it indicates the pressure against which the heart has to pump blood. Other

clinical end-points employed include change in WHO functional class. In addition, imaging studies could be used as secondary end-points to supplement the comparison.

Pipeline products

Most pipeline drugs for PAH are improvements from the three existing drug classes: ETRAs, prostacyclin analogues and PDE-5 inhibitors. Actelion's macitentan is a dual endothelin receptor antagonist that recently completed Phase III development. Results from the recent SERAPHIN trial were strongly positive and indicate strong efficacy with a favourable side effect profile. Actelion expect to submit the drug for regulatory approval in 2H12.

Companies are also attempting to develop orally administered drugs that work via the prostacyclin pathway. Oral prostacyclin analogues were first studied with Astellas' beraprost, which was abandoned due to lack of efficacy. United Therapeutics is now developing an oral treprostinil sustained release formulation for twice-daily administration and has submitted a NDA in December 2011. Actelion is also investigating an oral prostacyclin analogue, selexipag. Phase II data suggested efficacy equal to or better than inhaled prostacyclins and further phase III data will be available in 2013.

Bayer's Riociguat uses a novel approach to cGMP driven vasodilation. While the PDE-5 inhibitors are dependent on nitric oxide to stimulate initial formation of cGMP from its precursor, riociguat directly increases the sensitivity of the guanylate cyclase, the enzyme responsible for this conversion. As nitric oxide synthesis in some PAH patients has been found to be faulty, bypassing this mediator could prove to have higher efficacy than that seen with PDE-5 inhibitors. Results from small phase II studies appear favourable compared with existing oral PAH drugs phase III trials are due to report in 2H12.

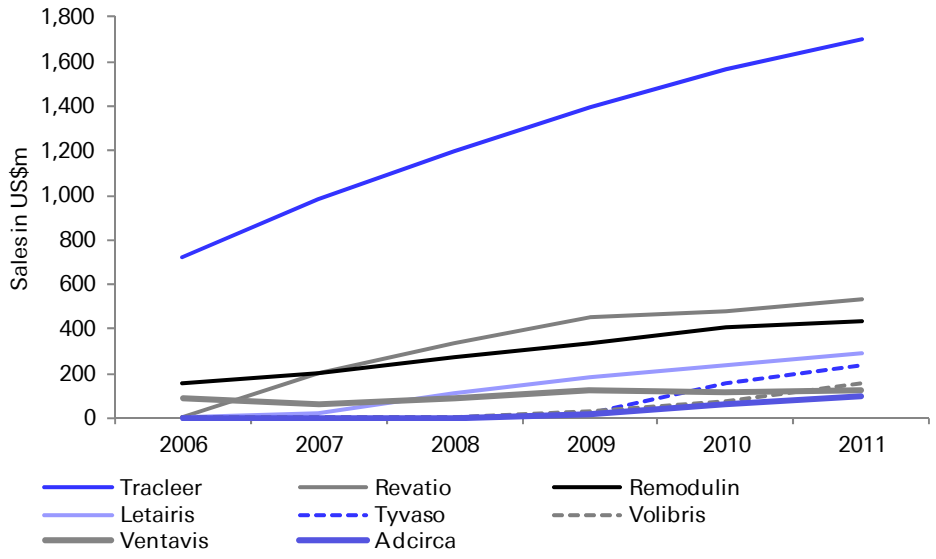
Figure 163: Select late stage pipeline products for PAH

Name	Company	Generic	Phase
Treprostinil sustained release	United Therapeutics	treprostinil	Filed
Macitentan	Actelion	macitentan	Phase III
Riociguat	Bayer	riociguat	Phase III
Selexipag	Actelion	selexipag	Phase III

Source: Deutsche Bank, Company data

Sales

Figure 164: Sales of key PAH drugs



Source: Deutsche Bank

Figure 165: Sales of key PAH drugs

Name	Company	2006	2007	2008	2009	2010	2011
Tracleer	Actelion	718	983	1195	1391	1563	1704
Revatio	Pfizer	0	201	336	450	481	535
Remodulin	United Therapeutics	152	201	270	332	404	430
Letairis	Gilead Sciences	0	21	113	184	240	293
Tyvaso	United Therapeutics	0	0	0	20	152	240
Volibris	GlaxoSmithKline	0	0	0	30	71	156
Ventavis	Actelion	93	65	88	126	114	120
Adcirca	United Therapeutics	0	0	0	16	59	101
Veletri	Actelion	0	0	0	0	3	17

Source: Deutsche Bank

Diabetes mellitus

- An estimated 366 million people have diabetes worldwide. By 2030, that number could grow to 552 million.
- In 2011, sales of diabetic drugs, including insulin, totalled c.$35bn.
- Leading companies include Novo Nordisk, Sanofi, Eli Lilly, Takeda and Merck.

Diabetes mellitus is estimated to affect more than 5% of the population in the developed world. In North America alone, more than 23 million people suffer from the disease, with a quarter of the affected asymptomatic and undiagnosed. In developing economies, where obesity and a sedentary lifestyle are growing in prevalence, the incidence of diabetes is increasing at a rate near 5% per annum, although this may be conservative if we consider the changing diet and lifestyle in emerging economies such as China. In addition to those who have diabetes, a further 344 million worldwide suffer from impaired glucose tolerance (IGT), 40-50% of whom will ultimately progress to diabetes.

Physiology

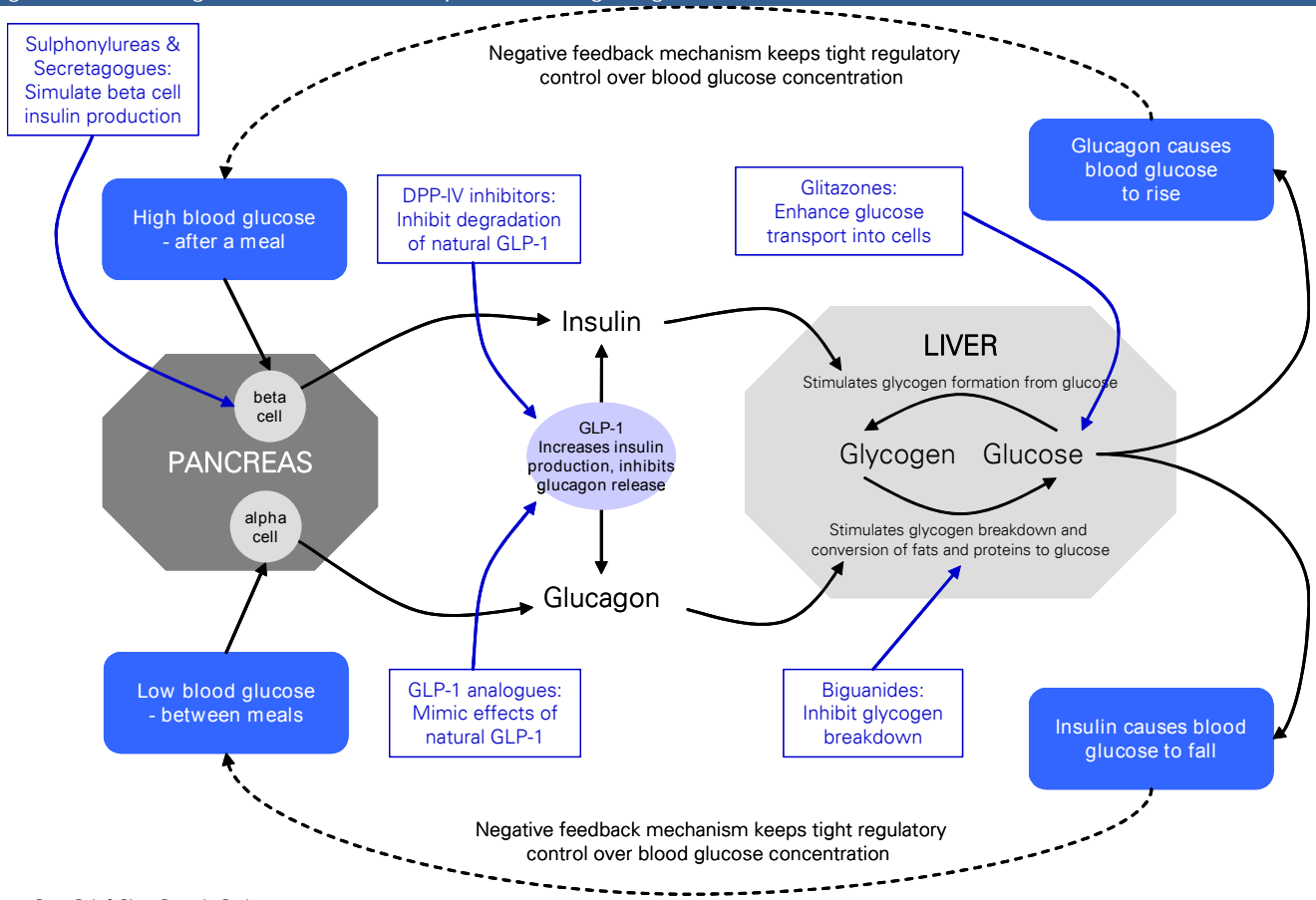
Diabetes is a chronic progressive metabolic disorder characterised by poor blood glucose control due to insulin deficiency and/or insulin resistance. Glucose is the primary fuel of cells. In healthy individuals, two principal glucose-regulating hormones (insulin and glucagon) maintain a constant blood glucose concentration in both the fasting and post-meal (post-prandial) state. When blood glucose levels are abundant, such as after eating a meal, insulin is released. Produced by cells in the pancreas, called beta cells, it encourages the uptake, utilisation and storage of glucose in muscle and fat tissues, but mainly in the liver. This reduces the level of glucose in the blood. During fasting, when the glucose level in the blood is low, insulin output falls and, among others, a counter-regulatory enzyme, glucagon, is released. Also produced in the pancreas but by alpha cells, glucagon stimulates the release of glucose into the blood from the liver by breaking down glucose stores called glycogen and converting other fuel sources such as fats and proteins into glucose. Figure 166 below attempts to explain these complicated relationships.

In a healthy body, blood glucose levels rise and fall within a fairly tight range of 70-110mg/dl. However, with diabetic insulin deficiency and/or resistance, blood glucose can rise to substantially higher concentrations, resulting in hyperglycaemia. Hyperglycemia, per se, is not a disease, but left untreated, it may lead to other issues, which can be broadly classified into microvascular and macrovascular complications.

- Microvascular complications, classified as disease affecting the small blood vessels, affect organs such as the nerves, eye and kidney glomeruli, causing neuropathy (nerve death and pain), blindness and kidney failure, respectively. It is also responsible for sores and ulcers on patients' legs/ feet and can result in amputations. Microvascular complications are thought to arise as a result of reactive oxygen species which form in the lining of small blood vessels as a result of hyperglycaemia. This leads to a narrowing and eventual occlusion of the vessel over time. HbA1c (which will be discussed later), a measure of the level of blood sugar control over the previous few months, is highly correlated with the risk of developing microvascular complications.

- Macrovascular complications refer to disease affecting the larger blood vessels. Diabetes is a key risk factor in atherosclerosis, the narrowing of blood vessels supplying organs such as the heart, brain and lower limbs. This is thought to occur as a result of increased free fatty acid oxidation in the lining of large vessels. This leads to production of the same reactive oxygen species, albeit by a different mechanism, but resulting in similar damage to the blood vessel lining, starting the cascade of events leading to plaque formation and vessel narrowing in the large blood vessels.

Figure 166: Blood glucose is controlled by insulin and glucagon



Source: Rang, Dale & Ritter, Deutsche Bank

There are generally two types of diabetes mellitus:

- **Type 1 diabetes**, or insulin-dependent diabetes (IDDM), is a condition where there is an absolute shortage of insulin. This is a result of the patient's immune system attacking and killing the insulin-producing beta cells of the pancreas. Accounting for roughly 10% of cases, Type 1 diabetes sufferers are typically diagnosed at a young age and will require life-long treatment. Given Type 1 patients' inability to produce insulin, treatment inevitably involves the injection of insulin.
- **Type 2 diabetes** accounts for approximately 90% of cases and occurs predominantly in people over the age of 40. In a majority of reported cases, patients are frequently overweight. The disease is most often characterised by impaired regulation of insulin secretion, and a resistance of peripheral tissues to insulin. Consequently, Type 2 diabetes is also known as non-insulin-

dependent diabetes mellitus (NIDDM); that is, insulin is produced but the body's insulin receptors are relatively insensitive to the levels of insulin in the body. As a result, the insulin-producing beta cells are forced to over-compensate, with the frequent result that, over time, insulin production gradually deteriorates (the beta cells 'burn out'). About 30% of NIDDM patients eventually become dependent on insulin.

Other factors are involved in modulating the levels of insulin production and secretion. For example, incretin hormones, e.g., GLP-1 and GIP (glucose-dependent insulinotropic peptide), are produced in the intestine in response to food, and signal the beta cells to increase their release of insulin and inhibit glucagons release by alpha cells. This plays an important role in controlling the surge in post-meal (post-prandial) glucose levels. These incretin hormones are naturally broken down by an enzyme called dipeptidyl peptidase-IV.

Pharmacological treatment

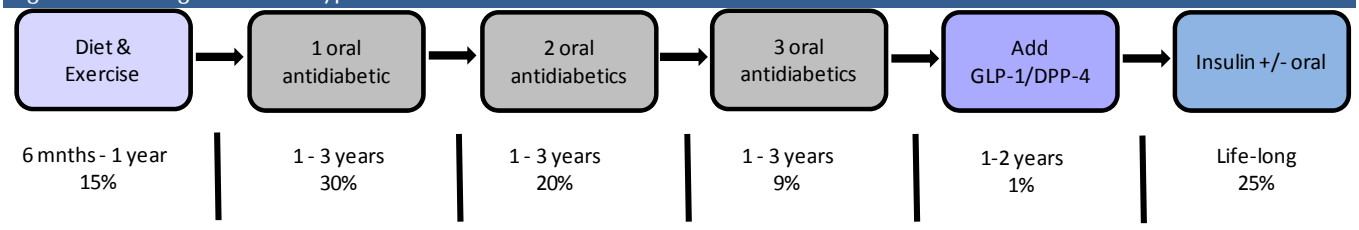
Diabetes is not yet curable, but can be controlled. The goals of diabetes management are to attain and maintain a near-normal blood sugar level, and reduce the risk of complications.

In Type 1 diabetes, treatment depends on the individual's needs, but typically consists of an insulin regimen, which at present requires the regular injection of differing formulations of insulin. This often comprises daily injections of long-lasting insulin to provide a basal level similar to that of the normal body, together with separate injections of rapid/intermediate acting product to provide a 'top-up' at meal times.

For Type 2 diabetics, treatment initially focuses on diet and exercise, as the loss of weight in obese patients helps to reduce the degree of insulin resistance. If this is insufficient, a range of oral medication may be started. Medication usually works by addressing one or several of the issues of Type 2 diabetes, e.g., reducing peripheral insulin resistance, reducing glucose production by the liver or increasing insulin secretion.

It should also be noted that diabetes is a progressive disease, where insulin resistance and ongoing beta cell death result in the patient progressing from a single oral therapy, to multiple oral therapies, to finally requiring insulin. At the time of diagnosis, only about 50% of pancreatic beta-cell function would remain, and this is estimated to continue to decline at an average of 4% a year. About 50% of patients will require more than one anti-diabetic medication by three years after their initial diagnosis, and this increases to 75% at nine years.

Figure 167: Progression of Type 2 diabetes



Source: Deutsche Bank

At present, there are six main classes of oral medication available, the main features of which are highlighted in Figure 168.

Figure 168: Therapies for Type 2 diabetes mellitus

Drug class	Sulphonylureas	Biguanides	Glitazones	Meglitinides	Alpha-glucosidase inhibitors	GLP-1 agonists	DPP-4 antagonists
Sales 2011 ($)	$1.5bn	$0.8bn	$4.3bn	$0.8bn	$1.0bn	$1.8bn	$5.1bn
Dose per day	One-three	Two-three	One-two	Per meal	Three	One-two	One
Risk of hypoglycaemia	High	Low	Low	Low	Low	Low	Low
Increased body weight	Yes	No	Yes	No	No	No	No
Reduction in lipids	No	Yes	Yes	No	No	No	No

Source: Company data, Deutsche Bank, EvaluatePharma

Sulphonylureas

First developed in the 1950s, sulphonylureas account for more than 25% of the oral diabetes market by volume. However, because they are now largely generic, they comprise only 4% of the market by sales. Sulfonyureas stimulate beta cells to increase insulin production rather than by sensitising the body to insulin. Overdosage may, however, cause hypoglycaemia (low blood sugar), which in severe cases, can result in coma or death if not rapidly treated. In addition, constant stimulation of the pancreas may hasten the eventual 'burn-out' of beta cells, potentially speeding the disease progression towards insulin dependence. Leading sulphonylureas include Diamicron (Servier), Amaryl (Sanofi) and Glipizide (Pfizer), all of which now suffer from generic competition.

Biguanides (Metformin)

Biguanides act by suppressing the breakdown of glycogen in the liver and enhancing glucose uptake in skeletal muscle (re-sensitisation). As they do not stimulate insulin production, they have a lower risk of hypoglycaemia compared to sulphonyureas. Side effects include stomach upset and, in rare cases, lactic acidosis. The most commonly prescribed drug in this class is metformin, the generic version of Bristol-Myers Squibb's glucophage. Metformin is believed to be the best initial treatment for newly diagnosed Type 2 diabetes.

Meglitinides

As with the sulphonylureas, meglitinides stimulate beta cells to produce insulin. However, both the onset and offset of insulin production are more rapid, thereby more accurately replicating the body's own insulin profile, an advantage over the sulphonylureas. The drug is taken at mealtimes and risk of hypoglycaemia is less than with sulphonylureas. At present, there are only two FDA approved drugs in this class, Novo Nordisk's Prandin/NovoNorm and Novartis' Starlix, both subject to generic competition.

Alpha-glucosidase inhibitors

This is a small class of drugs that works by blocking the absorption of carbohydrates in the small intestine, thereby reducing the post-meal spike in blood glucose level. Side effects include flatulence, diarrhoea and abdominal pain. Examples of products in this class are Bayer's Glucobay/Precose, Pfizer's Glyset and Takeda's Basen.

Glitazones

Also known as peroxisome proliferator-activated gamma receptor (PPAR-γ) agonists, these represent a class of compounds that act as insulin sensitizers, with low risk of causing hypoglycaemia when used alone. However, their major limiting side effects include oedema (retention of fluid in the limbs) and weight gain. There are currently two key marketed glitazones, namely Actos (Eli Lilly/Takeda) and Avandia (GlaxoSmithKline). In 2007, meta-analysis of 42 randomized trials involving Avandia (rosiglitazone) suggested that the drug may be associated with a significant increase in cardiovascular

events. In addition, a large trial called RECORD demonstrated no additional CV risk but did show an increased risk of heart failure with Avandia, although there have been criticisms surrounding the conduct of the trial. The FDA has mandated a black box warning of these risks on both Actos and Avandia. Most of the concerns have centred on Avandia, and sales of this drug have suffered since the warning was issued in 2007. Since November 2011, Avandia is restricted to healthcare providers and patients enrolled in the 'Avandia-Rosiglitazone Medicines Access Program' in US. Avandia authorization was suspended by EMA in September 2010. Actos safety reviews found that more than one year of use could be associated with bladder cancer and a warning was added to the FDA approved label in April 2011.

Glucagon-like peptide 1 analogues (GLP-1 analogues)

A number of companies are focused on the glucagon-like peptide 1 (GLP-1) pathway which is responsible for increasing insulin release and inhibiting glucagon secretion. Advantages of this class include strong efficacy with low risk of hypoglycaemia, as insulin is released only in the presence of high glucose levels (e.g., following a meal), and a benefit of weight loss. Disadvantages, however, include various side effects including initial nausea, and the fact that it has to be administered as an injection.

GLP-1 in its natural form has a very short half-life and thus more stable analogues have been developed which extend the duration of action by avoiding enzymatic degradation. Eli Lilly and partner Amylin market Byetta (exenatide), which was the first drug in this class. Novo Nordisk's Victoza (liraglutide) was launched later, and offers the benefit of once-a-day dosing vs. twice a day in Byetta. Once-weekly Bydureon (extended-release exenatide) was approved by the FDA in 2011. This class of drugs is generally quite safe, however, it has been associated with gastrointestinal (GI) side effects, and cases of necrotizing pancreatitis, and Victoza and Bydureon were approved with FDA black box warnings about their association with thyroid C-cell tumours.

Dipeptidyl peptidase 4 (DPP-4) inhibitors

DPP4 is an enzyme which breaks down GLP-1; hence, drugs which inhibit the DPP-4 enzyme result in higher levels of GLP-1. Currently Merck's Januvia (sitagliptin), Bristol-Myers Squibb/AstraZeneca's Onglyza (saxagliptin) and Eli Lilly/Boehringer Ingelheim's Trajenta (linagliptin) have been approved in both the US and EU markets. Novartis' Galvus (vildagliptin) has been launched in Europe, but not in the US, where Novartis withdrew its application following the FDA's request for additional studies. Post-marketing data had suggested an increased incidence of pancreatitis associated with Januvia, though the link was not strong enough to warrant a black box warning or withdrawal. Overall, this class of drugs is more convenient than GLP-1s (oral and low nausea), but offers lower efficacy and only limited weight loss.

Figure 169: Leading therapies for Type 2 diabetes in 2011

Name	Generic	Company	Class	Sales 2011 ($)
Actos	pioglitazone	Abbott/Takeda	glitazone	$4.1bn
Januvia	sitagliptin	Merck	DPP-4 antagonist	$3.7bn
Victoza	liraglutide	Novo Nordisk	GLP-1 agonist	$1.1bn
Galvus	vildagliptin	Novartis	DPP-4 antagonist	$0.7bn
Byetta	exenatide	Amylin/Eli Lilly	GLP-1 agonist	$0.7bn
Amaryl	glimepiride	Sanofi	Sulphonylurea	$0.7bn

Source: Company data, Deutsche Bank, EvaluatePharma

Insulin

In the case of Type 1 patients and around one-third of Type 2 patients, insulin becomes the mainstay of therapy. In 2011, global sales of insulin totalled c.$17.4bn. The insulin

market has three dominant players – Novo Nordisk, Sanofi, and Eli Lilly that account for c.99% global insulin sales.

Therapeutic insulin was first extracted from the pancreas of pigs (porcine) and cows (bovine) and purified for human use. They are very similar to human insulin (porcine insulin differs from human insulin by one amino acid, bovine insulin differs by three amino acids), and exert a similar physiological effect following injection. However, due to their animal origins, they were frequently associated with side effects such as allergic reactions. Since then, recombinant human insulin (human insulin produced by bacteria) has largely replaced animal-derived insulin.

Human insulin has a natural half-life of around four to six hours. In order to more closely replicate the body's physiological profile of insulin levels, different methods have been used to change the pharmacokinetic profile of insulin. These include the use of additives, e.g., crystalline zinc to extend the duration of action. Later, insulin analogues were produced, which are genetically modified forms of human insulin that exert a similar effect on insulin receptors but have been modified to have a different onset of action and duration in the body.

The insulin market can primarily be broken down into three categories:

- **Short-acting insulin**: Conventional short-acting insulin, including Eli Lilly's Humulin R and Novo Nordisk's Novolin R, are short-acting formulations which are taken before meals to moderate the post-meal increase in glucose levels. Eli Lilly and Novo Nordisk have introduced short-acting analogues, namely Humalog (insulin lispro) and Novolog (insulin aspart), which provide a faster onset of action and faster offset.
- **Long-acting (NPH or basal) insulin**: Humulin N (NPH insulin) and Novolin N are long-acting insulin formulations with a duration of action of approximately 16-18 hours, thus requiring twice daily dosing. They provide a steady level of background insulin without any mealtime peaks and are usually used in combination with a short-acting insulin or short-acting analogue. Sanofi's Lantus (insulin glargine), launched in 2000, was the first true long-acting insulin analogue. Lasting a full 24 hours, it is the only product requiring a true once daily dosing. Novo Nordisk has also since developed a basal insulin analogue, Levemir (insulin detemir), which was launched in Europe in 2004 and in the US in 2006. However, Levemir does not have quite as long a duration of action as Lantus and is often prescribed as twice-daily doses.
- **Premixes**: Premixes, such as Humulin 70/30 and Novolin 70/30, are pre-mixed combinations of short- and long-acting insulin (Eli Lilly's Humalog 75/25 is a pre-mix incorporating a long- and a short-acting analogue). They are administered two or three times daily and provide the benefit of containing both short-acting and basal insulin in a single dose, without having to be reconstituted separately. More recently, mixes of newer short-acting and long-acting insulin analogues have been formulated (e.g., NovoMix), offering the benefits of a smoother insulin profile with the newer insulins in single-dose device.

Inhaled insulin formulations

Inhaled rapid-acting insulin formulations reduce the need for injections to control the meal-time spike in blood glucose levels. Pfizer had introduced Exubera, its inhaled recombinant human insulin, in 2006, but withdrew the product in 2007 as sales failed to materialize and potential safety signals mounted. The device that delivered the inhalant

was cumbersome and efficacy was comparable to injectable fast-acting insulin formulations. MannKind filed for approval of its inhaled insulin product Afrezza in December 2010, but approval has been delayed as the FDA has requested additional clinical trials.

Figure 170: Leading insulins in 2011

Name	Generic	Company	Sales 2011 ($)
Lantus	insulin glargine	Sanofi	$5.5bn
Human insulin & devices	Human insulin	Novo Nordisk	$2.4bn
NovoRapid	insulin aspart	Novo Nordisk	$2.4bn
Humalog	insulin lispro	Eli Lilly	$2.4bn
NovoMix 30	insulin & insulin aspart	Novo Nordisk	$1.5bn
Levemir	insulin detemir	Novo Nordisk	$1.4bn
Humulin	Human insulin	Eli Lilly	$1.2bn
Apidra	insulin glulisine	Sanofi	$0.3bn
Insuman	Human insulin	Sanofi	$0.2bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Clinical end-points

The main objective of Type II diabetes treatment is the reduction of complications through the control of blood glucose levels. However, as diabetes typically develops complications over a number of years, it is impractical to require new drugs to show these benefits. As such, a surrogate marker is used. One such marker is glycosylated haemoglobin (HbA1c) levels. Haemoglobin, the oxygen-carrying protein in red blood cells, is glycosylated (has a glucose molecule attached to it) when blood glucose levels are high. As the lifespan of red blood cells is about 120 days, the percentage of HbA1c in the blood is considered a proxy for monitoring abnormal spikes in blood glucose, and hence overall diabetic control over the previous three to four months. In non-diabetics, HbA1c levels are typically less than 6%, whereas in diabetics, they are typically over 8%. Current ADA (American Diabetes Association) guidelines recommend that treatment of diabetes should target HbA1c levels of less than 7%.

The Diabetes Control and Complications Trial (DCCT) and the UK Prospective Diabetes Study (UKPDS) have shown that tight control of HBA1c is able to reduce the risk of microvascular complications, while other studies suggest a link between post-prandial (post-meal) glucose levels and atherosclerotic risk. Hence, HbA1c, pre- and post-meal glucose levels, and evidence of macrovascular (cardiovascular events) and microvascular complications are key end-points in assessing the efficacy of treatment in diabetes.

Partially spurred on by the safety concerns caused by Avandia, the FDA now also requires companies to disprove cardiovascular harm prior to approval. If harm cannot be ruled out, the FDA may require the company to conduct either pre- or post-marketing studies (based on the level of certainty provided at the initial review).

Pipeline products

Dual PPAR agonists

Several dual-PPAR agonists are currently in late-stage development. These drugs act upon the PPAR-gamma receptor, which is associated with increased insulin sensitivity and reduced glucose levels as well as the PPAR-alpha receptor, which is associated with reduced triglycerides and increased HDL cholesterol. Earlier candidates in this

class, such as Bristol-Myer's muraglitazar, and AstraZeneca's tesaglitazar were high-profile, late-stage failures. The latest drug in development, Roche's aleglitazar, shows promising early results and is currently in Phase III trials.

SGLT-2 inhibitors

Sodium-dependent glucose co-transporter (SGLT) inhibition is a novel therapy which shows promise and is potentially complementary to other diabetic medications. SGLT is a protein which transports glucose across the apical membrane of the intestine (SGLT-1), or the renal filtrate (SGLT-2) into the bloodstream. Therefore, inhibition of this mechanism should result in lower glucose absorption from the gut and renal filtrate, and hence lower blood glucose. SGLT inhibition is insulin-independent and thus appears to be a candidate for add-on therapy. SGLT-2 inhibitors in development include Bristol-Myers Squibb/AstraZeneca's Forxiga (dapagliflozin), Johnson & Johnson's canagliflozin, Boehringer Ingelheim's empagliflozin, Astella's ipragliflozin and Roche/Chugai's tofogliflozin. The FDA issued a complete response letter for Forxiga to BMS/AstraZeneca in January 2012 requesting additional data, though the drug received a positive CHMP opinion in April 2012. Lexicon is developing a dual SGLT-1/2 inhibitor (LX 4211), currently in phase II trials.

GLP-1 analogues

A number of drug companies are developing long-acting GLP-1 analogues which are administered once weekly. These include GlaxoSmithKline's albiglutide (Syncria, Phase III), Eli Lilly's dulaglutide (Phase III) and Novo Nordisk's semaglutide (Phase II). Sanofi's lixisenatide (Phase III) is administered once daily, but the company hopes that it can be used in a once-daily combination with its long-acting insulin, Lantus.

Long-acting insulin analogue

Novo Nordisk has filed for approval of two insulin analogues: Tresiba (degludec) and Ryzodeg. Tresiba is a long-acting insulin analogue with a potential smoother profile, lower incidence of hypoglycemia and once-daily any time dosing. Ryzodeg is a combination of degludec and insulin aspart, which aims to achieve a smoother basal once-daily profile and provide both fasting and post-prandial glucose control. Eli Lilly is also developing a long-acting basal insulin (LY2605541, Phase II) with additional weight loss benefits, and a new insulin glargine copy product (Phase III).

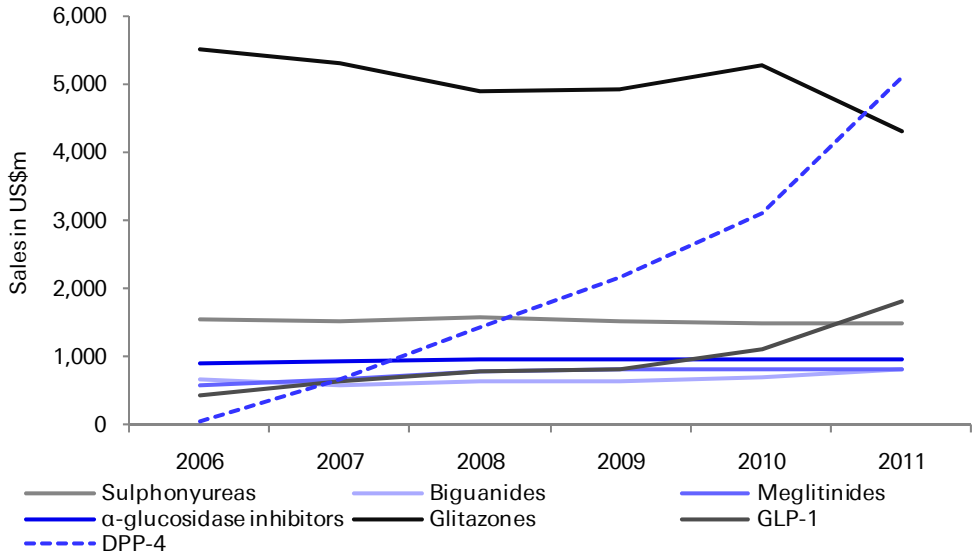
Figure 171: Selected late-stage pipeline products for diabetes

Name	Company	Class	Status
Tresiba	Novo Nordisk	Basal Insulin	Filed
Ryzodeg	Novo Nordisk	Basal Insulin + rapid acting insulin	Filed
Afrezza	MannKind	Inhaled insulin	Filed
Lyxumia	Sanofi	GLP-1 agonist	Filed
Forxiga	Bristol-Myers Squibb/AstraZeneca	SGLT-2 inhibitor	Filed
Dulaglutide	Eli Lilly	GLP-1 agonist	Phase III
Albiglutide	GlaxoSmithKline	GLP-1 agonist	Phase III
New insulin glargine product	Eli Lilly	Insulin	Phase III
Canagliflozin	Johnson & Johnson	SGLT-2 inhibitor	Phase III
Empagliflozin	Boehringer Ingelheim	SGLT-2 inhibitor	Phase III
LY2605541	Eli Lilly	Basal Insulin	Phase III
Ipragliflozin	Astellas Pharma	SGLT-2 inhibitor	Phase III
Aleglitazar	Roche	Dual PPAR agonist	Phase III
Tofogliflozin	Chugai	SGLT-2 inhibitor	Phase III
Semaglutide	Novo Nordisk	GLP-1 agonist	Phase II
LX4211	Lexicon	SGLT1/2 inhibitor	Phase II

Source: Company data, Deutsche Bank, EvaluatePharma

Sales

Figure 172: Sales of non-insulin diabetes therapies



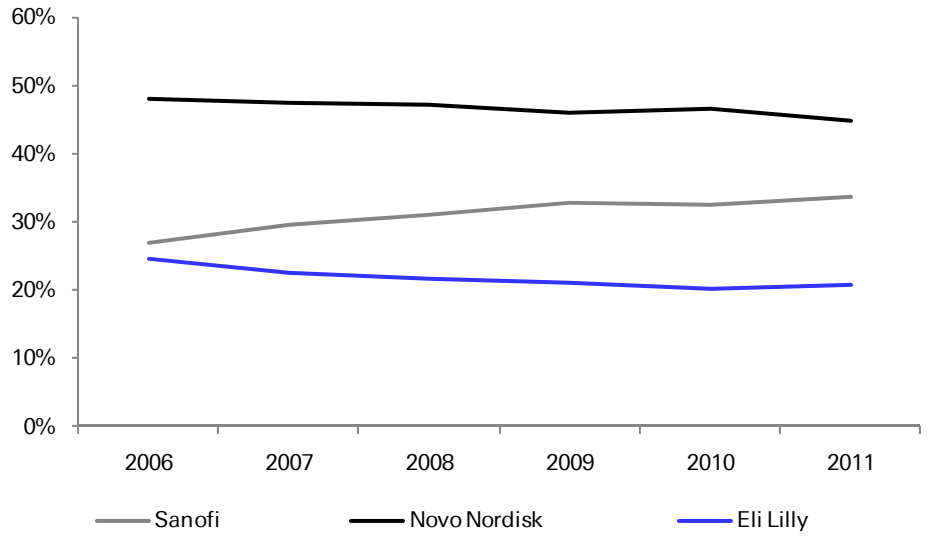
Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 173: Sales of non-insulin diabetes therapies ($ m)

Class	2006	2007	2008	2009	2010	2011
Sulphonyureas	1,546	1,523	1,566	1,507	1,501	1,481
Biguanides	666	590	653	635	686	813
Meglitinides	587	658	781	825	823	820
α-glucosidase inhibitors	901	928	975	975	968	970
Glitazones	5,512	5,299	4,896	4,917	5,281	4,293
GLP-1	430	650	775	813	1,123	1,804
DPP-4	43	676	1,440	2,158	3,117	5,093

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 174: Insulin market share



Source: Company data, Deutsche Bank, EvaluatePharma

Figure 175: Insulin market share

Company	2006	2007	2008	2009	2010	2011
Sanofi	27%	29%	31%	33%	33%	34%
Novo Nordisk	48%	47%	47%	46%	47%	45%
Eli Lilly	24%	22%	22%	21%	20%	21%

Source: Company data, Deutsche Bank, EvaluatePharma

Erectile dysfunction

- 150 million men are affected by ED worldwide, with prevalence likely to double by 2025.
- Sales of PDE-V inhibitors, comprising Viagra (Pfizer), Cialis (Lilly), and Levitra (Bayer), reached c.$4.3bn in 2011.

An estimated 30 million men in the US and as many as 150 million men worldwide experience erectile dysfunction (ED), defined as the inability to achieve and maintain an erection adequate for satisfactory sexual intercourse. Causes of ED may be either physiological, psychological, or (in the majority of cases) a combination of both. While an overwhelming 70% of cases are associated with vascular disease, ED may also be caused by drug-related, operative, neurological, and other factors. In addition, ED often occurs as a consequence of normal aging, affecting as many as 50% of men between the ages of 40 and 70.

Physiology

When a man is sexually aroused, the arteries in the penis muscles, the corpora cavernosa, relax and widen, allowing more blood to flow into the penis. At the same time, the veins in the muscles compress, restricting the blood outflow. With increased blood flow in and reduced blood flow out, the penis enlarges, resulting in an erection.

On a cellular level, this process is more complex. Upon stimulation, the corpora cavernosa muscles release the neurotransmitter nitric oxide (NO). In turn, NO stimulates the enzyme guanylate cyclase, which facilitates the synthesis of cyclic guanine monophosphate (cGMP). Cyclic GMP triggers a cascade of reactions that relax the penile muscles, allowing the blood accumulation required for erection.

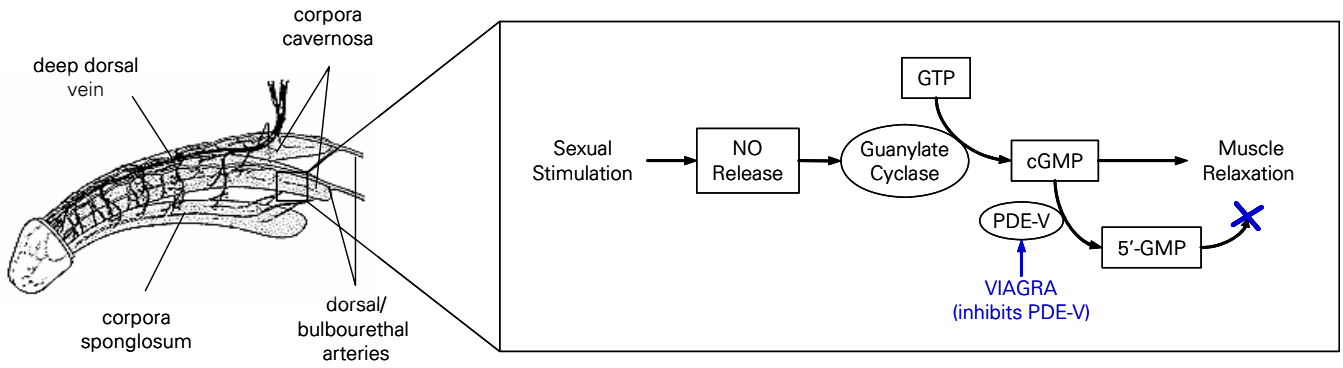
The natural regulator of this process is the enzyme phosphodiesterase type V (PDE-V). PDE-V inhibits erection by breaking down cGMP into a non-biologically active form, 5'-GMP. In the absence of cGMP, the body's signal to the corporate cavernosa is interrupted and the patient fails to achieve an erection.

Pharmacological treatment

Historically, ED was a relatively small market under the domain of urological specialists. Drug therapies, using compounds such as phentolamine, papaverine, and alprostadil, were either injected into the penis or delivered as urethral suppositories (inserted into the urinary opening). Sales of therapeutic drugs for ED only took off when Viagra (sildenafil) was launched in 1998.

Viagra, together with newer entrants Cialis and Levitra, is a PDE-V inhibitor, blocking the enzyme's ability to inactivate cGMP. However, the class has no effect on the initial release of NO. The implication of this is that Viagra can potentiate an erection once sexual stimulation has induced NO-release, but the drug cannot produce an erection on its own.

Figure 176: Mechanism of erection and action of PDE-V inhibitors



Source: National Institute of Diabetes & Digestive & Kidney Diseases, Deutsche Bank

Viagra's adverse effects are partly associated with its interaction with other members of the phosphodiesterase family. There are 11 PDE isoforms in the body, each of which plays an important role in other signalling pathways. Viagra appears to be many thousand-fold more selective for PDE-V than for most other PDE isoforms, including PDE-III, an isoform involved in the control of cardiac contractility. However, Viagra's selectivity for PDE-V versus PDE-VI (an isoform found in the retina) is only tenfold greater, most likely forming the basis for colour vision disturbances seen in some patients. Both Levitra and Cialis avoid this side effect due to their greater selectivity for the PDE-V isoform.

More importantly, the PDE-V inhibitors have been shown to enhance the hypotensive (blood-pressure lowering) effects of nitrate drugs which may be taken for heart conditions. Thus, they are contraindicated in this group of patients and are additionally discouraged in men with a recent history of coronary heart disease.

Figure 177: PDE-V inhibitors for erectile dysfunction

Name	Generic	Company	2011 Sales ($)
Viagra	Sildenafil	Pfizer	$2.0bn
Cialis	Tadalafil	Lilly / ICOS	$1.9bn
Levitra	Vardenafil	Bayer / Merck / GSK	$0.5bn

Source: Deutsche Bank, EvaluatePharma

Clinical end-points

The severity of ED is typically evaluated using the International Index of Erectile Function (IIEF) and the Sexual Encounter Profile (SEP), standardised questionnaires comprising a series of questions concerning sexual function. The IIEF Erectile Function domain has a 30-point total score, measuring before and after treatment. Two of the SEP questions usually serve as primary end-points, namely, those regarding: 1) the ability to achieve erections sufficient for sexual intercourse and 2) the maintenance of erections after penetration.

Figure 178: Efficacy and pharmacokinetic data for PDE-V inhibitors

	Viagra (50 mg)	Cialis (20 mg)	Levitra (20 mg)
Producer	Pfizer	Lilly	Bayer/Schering-Plough/GSK
Generic	sildenafil	tadalafil	vardenafil
% erection sufficient for penetration (placebo)	74% (24%)	62% (39%)	80% (52%)
% maintenance of erection (placebo)	66% (20%)	50% (25%)	65% (32%)
Tmax (hours)	1	2	0.7
T½ (hours)	4	17.5	4-5
Selectivity for PDE-V vs. PDE-III	4,000x	44,000x	3,600x
Side effects	headache, flushing, dyspepsia, rhinitis, abnormal vision	dyspepsia, back pain, dizziness, myalgia	headache, flushing, rhinitis, dyspepsia

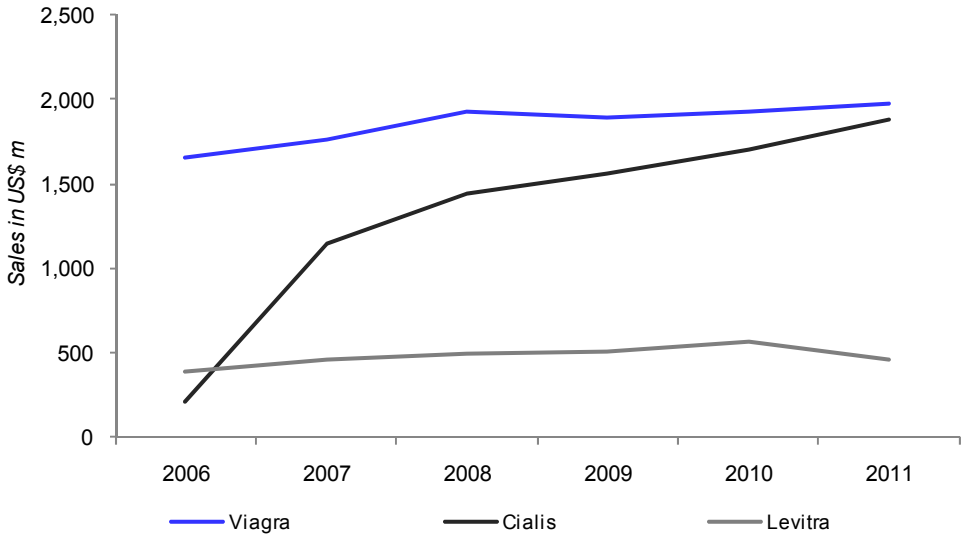
Note: All PDE-V inhibitors are contraindicated in patients with heart conditions who are taking or expect to take nitrates.
Source: Company data

Pipeline products

Given that Viagra, Cialis, and Levitra provide an effective and convenient treatment for ED, there is currently little in the development pipeline. Sales of this class are expected to decline in the coming years as these drugs lose patent protection, starting with Viagra in 2012.

Sales

Figure 179: Sales of key ED drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 180: Sales of key ED drugs ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Viagra	Pfizer	1,657	1,764	1,934	1,892	1,928	1,981
Cialis	Eli Lilly	216	1,144	1,445	1,559	1,699	1,876
Levitra	Bayer	395	455	501	502	569	462

Source: Company data, Deutsche Bank estimates, EvaluatePharma

GERD and peptic ulcer disease

- Sales of drugs treating gastric ulcers and GERD totalled c.$15bn in 2011.
- c.30% of the US population is affected by GERD.
- The market is dominated by proton pump inhibitors, led by AstraZeneca's Nexium.
- Underlying prescription growth is strong but market value is in decline due to generic penetration.

Gastro-oesophageal reflux diseases (GERD) are disorders that arise as a consequence of stomach acid causing tissue destruction or irritation. GERD, or heartburn, refers to the backward flow of acid from the stomach up into the oesophagus, which, unlike the stomach, has no protective lining. Approximately 10% of Americans suffer from heartburn daily, with more than one-third of the population suffering intermittent symptoms. As such, heart burn is by far the most frequent disorder in this category. An ulcer is less frequent and is a focal area of the lining of the stomach or duodenum that has been destroyed by digestive juices and stomach acid, usually facilitated by the bacteria Helicobacter pylori (H. pylori). H. pylori is estimated to play a role in more than 90% of duodenal ulcers and around 80% of gastric ulcers. Peptic ulcers are also frequently caused by the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin, or from stress. Approximately 10% of Americans will develop a chronic peptic ulcer during their lifetime.

Physiology

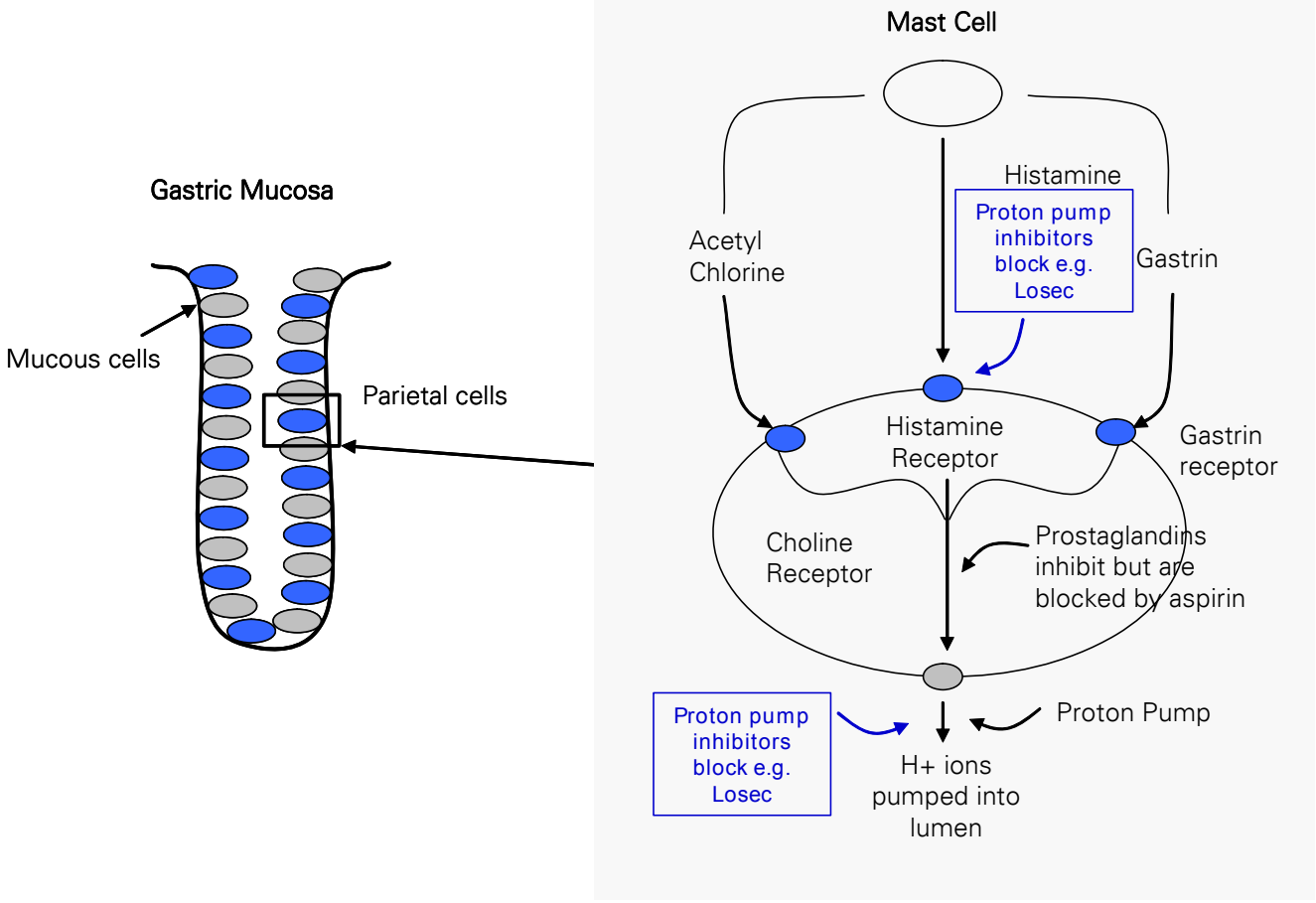
The stomach secretes c.2.5 litres of gastric juice daily. The principal secretions are pepsinogens (used to break down proteins) and hydrochloric acid (which serves to digest food). These are secreted by cells located in the stomach lining, called parietal cells. In addition, mucus is secreted by mucosal cells and forms an important buffer protecting the gastric lining (mucosa) from the acid in the gastric juices. Locally produced prostaglandins stimulate the production of mucus (hence, by inhibiting one of the enzymes in prostaglandin production, namely cyclooxygenase 1, NSAIDs such as aspirin and naproxen reduce prostaglandin levels and have a detrimental effect on the stomach).

In both peptic ulcers and GERD, the regulation of acid secretion by parietal cells is especially important. Parietal cells have proton pumps (also known as acid pumps) on their membranes, by which hydrochloric acid is secreted via active transport into the stomach cavity. The three main biochemical messengers that promote the activity of the proton pump are illustrated in Figure 181. They include:

- **Gastrin**, a peptide hormone, which is synthesised by endocrine cells in the stomach antrum. Its production is induced by the digestion of food in the stomach.
- **Acetylcholine**, which is released by nerve endings in the stomach upon the sight and smell of food.

- **Histamine** is released from mast cells, which are stimulated by both acetylcholine and gastrin. Histamine binds to histamine-2 receptors (called H2 receptors) on parietal cells and promotes acid production by the proton pump.

Figure 181: The parietal cell and factors affecting acid secretion



Source: Rang, Dale & Ritter , Deutsche Bank

Pharmacological treatment

In both GERD and peptic ulcers, one of the key aims of pharmaceutical therapy is to reduce or inhibit the production of acid. This is key to preventing the stomach from digesting itself and allowing the damaged area of the stomach lining to heal. The market is dominated by two main classes of drugs – H2 antagonists (for example, GSK's Zantac), which were first introduced in the 1970s, and proton pump inhibitors or PPIs (for example, AstraZeneca's Nexium), which arrived later.

Figure 182: Comparison H2 antagonists vs. PPIs

Class	H2 antagonists	PPIs
Estimated sales in 2011 ($)	$1.2bn	$12.4bn
Leading products	Zantac	Nexium
Point of action	Histamine receptors	Proton pump
Healing rates 4 weeks	56% gastric ulcers healed	78% gastric ulcers healed
Healing rates 8 weeks	78% healing	91% healing

Source: Deutsche Bank, EvaluatePharma

H2 antagonists

Histamine is one of the factors which stimulates the secretion of acid. These completely inhibit histamine-related acid secretion but only partially decrease gastrin and acetylcholine-related secretion (hence, they are less efficacious than PPIs). They are taken orally once or twice a day and are well tolerated. Side effects are limited, but include diarrhoea and dizziness. Most H2 antagonists are also available over-the-counter in many countries.

Proton pump inhibitors (PPIs)

The PPIs inhibit the proton pump in parietal calls, thereby blocking the production of acid. The first to market was Prilosec/Losec (omeprazole), which for several years was the world's best-selling drug but has since been completely overwhelmed by generics following the expiry of its patent in 2001. The product is taken orally, but because it rapidly degrades in acid, it is administered with a special coating to ensure its absorption into the blood. Side effects are limited but may include diarrhoea, headache, and sometimes rash. In recent years, sales of branded drugs in this class have suffered further generic erosion following the patent expiry of branded drugs including the blockbusters Prevacid and Protonix.

Because proton pump inhibitors directly inhibit acid production, they have proven significantly more efficacious than H2 antagonists in reducing acid levels, thereby increasing healing rates. Consequently, they account for a greater share of the market in volume terms.

Common OTC products

The FDA allows some drugs to be sold over-the-counter to relieve occasional acute heartburn symptoms: broadly categorized into antacids and acid reducers. Antacids act by neutralizing the acid already produced in the stomach, and relieve heartburn and stomach upset. Most available antacids are salts of magnesium, aluminum or calcium, or combinations thereof (magnesium and aluminum salts may be combined as they counteract each other's GI side effects). Sodium bicarbonate is available as a fast-acting alternative, but can aggravate symptoms by inducing further acid formation with regular use. Some combination products may also contain simethicone, which relieves flatulence. Long term use of antacids may result in electrolyte disturbances and kidney stones, among other side effects, and is not recommended.

Acid reducers are low-dose H2 antagonists and proton pump inhibitors, which act by interfering with the acid producing mechanism. The FDA allows these products to be sold as OTC drugs if it believes they can be self administered safely without a physician's guidance. Combinations of antacids and acid reducers are also available.

Antibiotics

As Helicobacter pylori plays a key role in causing chronic stomach ulcers, antibiotics are frequently also required to eradicate the bacterium. This is typically prescribed in combination with a proton pump inhibitor to promote healing of the ulcer. Triple therapy comprises two antibiotics (usually amoxicillin and clarithromycin) and a PPI, while bismuth subsalicylate is added to two antibiotics (metronidazole and tetracycline) and a PPI for quadruple therapy.

Clinical end-points

The key end-points used in clinical trials are typical rates of healing over different periods of time, compared with placebo. For gastric ulcers, the time periods are typically four and eight weeks. For GERD and duodenal ulcers, healing over four to

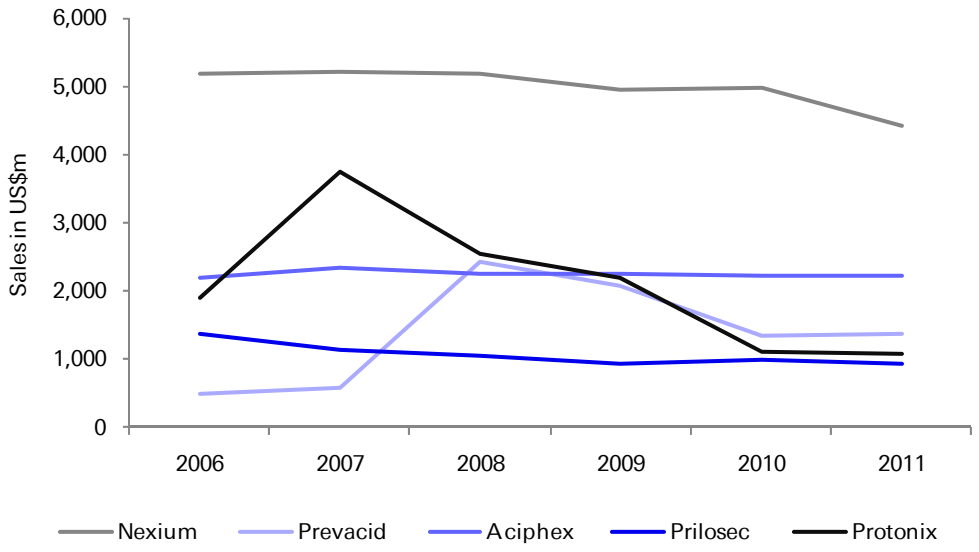
eight weeks is also measured. In addition, measures of stomach acidity over a set number of days may also be taken, although these are not indicative of healing rates.

Pipeline products

Current PPIs are highly effective, with minimal side effects, leaving little room for significant improvement. Moreover, the market continues to be hugely competitive, with the availability of generic drugs contributing to increased price competition across the class. Therefore, it is no surprise that the pipeline for gastrointestinal disorders is relatively thin and unexciting.

Sales

Figure 183: Sales of leading PPIs



Source: Company data, Deutsche Bank, EvaluatePharma

Figure 184: Sales of leading PPIs ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Nexium	AstraZeneca	5,182	5,216	5,200	4,959	4,969	4,429
Prevacid	Takeda	495	569	2,435	2,085	1,330	1,372
Aciphex	Eisai/ Johnson & Johnson	2,187	2,354	2,250	2,256	2,237	2,236
Prilosec	AstraZeneca	1,371	1,143	1,055	946	986	946
Protonix	Nycomed/ Pfizer	1,898	3,744	2,536	2,201	1,101	1,084

Source: Company data, Deutsche Bank, EvaluatePharma

Asthma

- Global sales of asthma-related medication totalled c.$17bn in 2011.
- 5-6% of the US population is affected (National Heart, Lung, and Blood Institute).
- Sales have grown at c.8% CAGR over the past 5 years, aided by improved diagnosis, newer drugs and more aggressive treatment.
- Complex delivery devices and bioequivalence difficulties afford protection beyond drug patent expiry.
- Leading companies include GlaxoSmithKline, AstraZeneca and Merck.

Asthma is defined as a reversible obstruction of the airways, usually triggered in response to an allergic reaction. An asthmatic person reacts to stimuli that are not of themselves noxious and suffers intermittent but recurrent attacks. The asthmatic experiences difficulty in breathing out resulting from a severe constriction of airways in the lungs (bronchospasm). Patients frequently have persistent cough and suffer mucus plugging of airways. Asthma is an increasingly common ailment globally, the incidence of which is believed to reflect increased industrialisation, air pollution, and urban living. According to WHO estimates, asthma is the most common chronic disease among children and afflicts more than 300 million people around the world. In the United States, the lifetime risk of asthma is around 13%, with about 10% of children below the age of 18 currently suffering from the disease.

Physiology

The characteristic features of asthma are inflammatory changes in the respiratory airways that are associated with abnormal bronchial (lung) sensitivity to allergens that are normally non-noxious. For example, pollen, or particles of house-mite dust can provoke an asthma attack. Indeed, even the 'shock' of cold air and exercise can bring on an attack. The development of asthma probably involves both genetic and environmental factors.

Current theory suggests that there are two main phases of an attack:

1. Initial response – sudden onset of bronchospasm in response to the allergen; this involves the constriction of the smooth muscle in the bronchi.

2. Delayed response – inflammation and swelling occurs hours later, following exposure to the allergen.

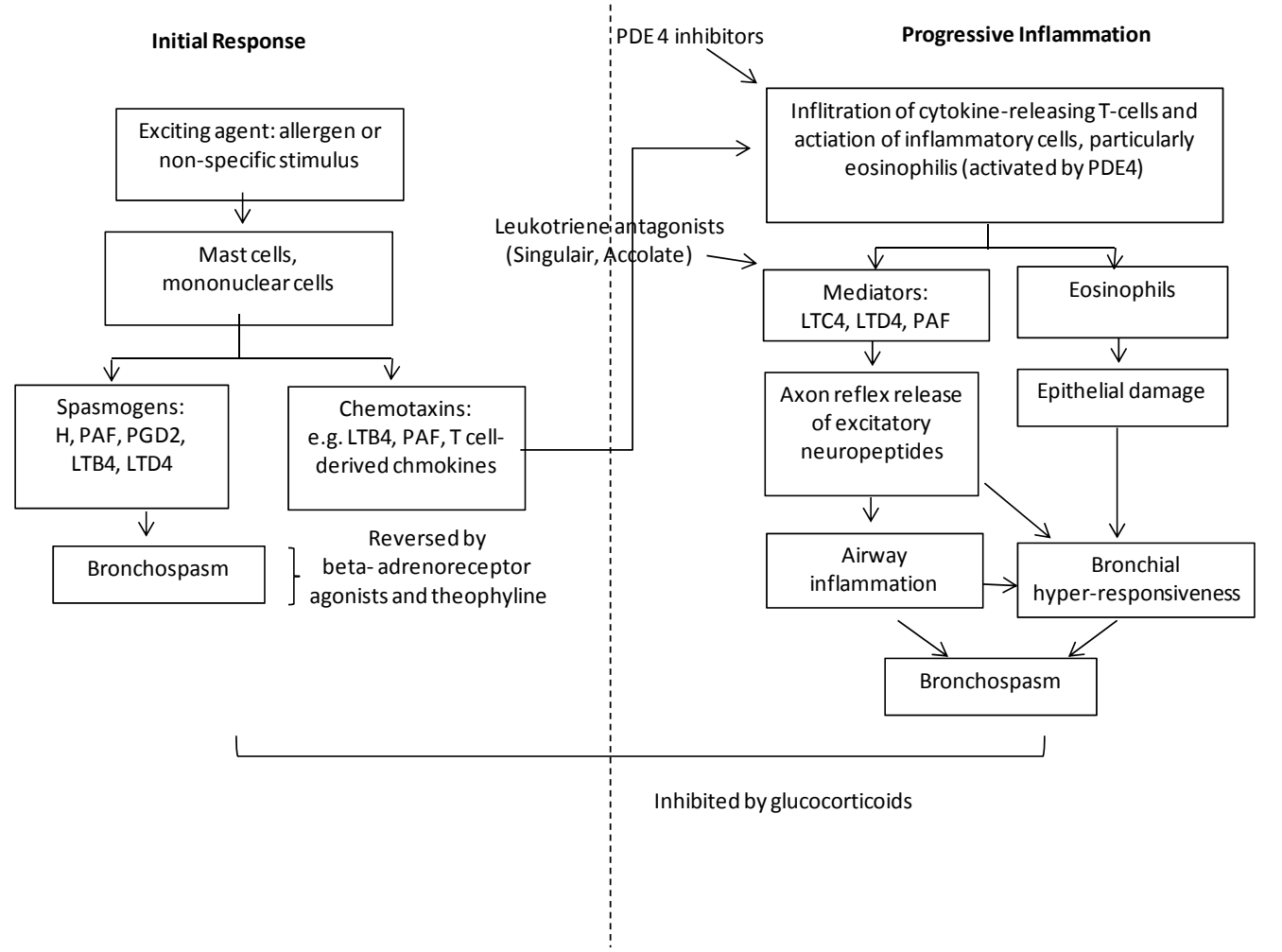
The inflammation associated with asthma is different from bronchitis, in that it is associated with the presence of white blood cells (T cells), which release chemical messengers (cytokines), which in turn release products that damage the airways.

In the initial response, bronchospasm arises as the allergen interacts with immune response cells called mast cells. These cells release histamines and other cytokines, which cause smooth muscle constriction, and perhaps more significantly, release potent bronchial-constrictors and inflammatory agents called leukotrienes. These attract white blood cells to the area, setting the scene for the delayed inflammation stage. Factors that activate and attract platelets (PAF) to the area are also released from mast

cells. Note that beta agonists are administered to treat this initial reaction, acting on beta-2 receptors located in the smooth muscle tissues of the airways to cause bronchodilation and improve air flow. This provides symptom relief but does not treat the inflammatory process.

In the second or delayed phase, specific types of white blood cells, called T-helper lymphocytes (Th) and eosinophils (also a type of white blood cell), are attracted by the cytokines released by mast cells. Specific molecules released by the eosinophils, which normally forms part of the body's defences, cause damage to the epithelial lining of the bronchi. The synthesis of many of the inflammatory media, including PAF, leukotrienes and prostaglandins, is initiated. This synthesis is inhibited by steroids (glucocorticoids). Thus, drugs based on glucocorticoids, e.g., prednisolone and fluticasone, form the main pharmaceutical approach for the long-term prevention and treatment of the inflammatory response in asthma. Figure 185 illustrates the pathways and chemical mediators involved in asthma.

Figure 185: The physiology of asthma



Source: Rang, Dale and Ritter , Deutsche Bank

Pharmacological treatment

With a broad range of products available, treatment guidelines have been developed over the years. The National Heart, Lung, and Blood Institute (NHLBI) updated its clinical practice guidelines on the treatment of asthma in 2007, and these provide a useful overview of the approach to treatment of asthma. The focus in the latest guidelines has been on assessing asthma control and stepping up or down therapy as appropriate.

Importantly, within the medical treatment of asthma is the desire of physicians to target treatment at the affected area, particularly given the use of steroids, which have many unwanted side effects in the rest of the body. As such, inhaled products, which act on the lung and are not absorbed in the rest of the body, are often preferred to those taken orally.

Asthma medications have traditionally been divided into two categories – medications that are taken to relieve the acute attack, and medications that are taken to reduce the frequency of recurrent attacks:

- Medications that provide quick relief of bronchospasm during asthma attacks are taken short-term and only during the acute phase of the attack. These include first-line treatments such as short-acting beta agonists (SABA) and alternatives such as anti-cholinergic drugs. These drugs are not recommended for regular use or use in isolation, as they do not treat the inflammatory aspect of asthma, and hence do not control the frequency of attacks.
- Medications that reduce the frequency of attacks encompass anti-inflammatory drugs, which are taken on a daily basis to reduce the chronic airway inflammation. Inhaled corticosteroids are the most effective in this category in improving asthma control and are the first-line of drugs to be prescribed. If this proves to be insufficient, long-acting beta agonists (LABA) are the first choice as an add-on therapy, followed by alternatives such as leukotriene receptor antagonists, or theophylline. Omalizumab (Xolair), a recombinant humanized antibody against the IgE antibody, is an injection that may have an added adjunctive benefit in patients who are poorly controlled despite being on inhaled corticosteroids and LABAs.

The following shows the various steps of progression in adding on or taking off a medication. However, it is important to note that the patient starts at the step of treatment which is appropriate to their severity at the point of diagnosis, and is then stepped up or down according to their response. For example, a patient presenting with moderate persistent asthma may start treatment at Step 3 with a short-acting beta agonist, an inhaled steroid, and a long-acting beta agonist.

- **Step 1:** Inhaled short-acting beta agonist.
- **Step 2**: Inhaled short-acting beta agonist, plus regular low-dose inhaled steroid (leukotriene antagonists and cromolyn are less preferred alternatives).
- **Step 3**: Inhaled short-acting beta agonist, plus regular high-dose inhaled steroid or regular standard dose inhaled steroid plus long-acting beta agonist.
- **Step 4**: Inhaled short-acting beta agonist, plus regular high-dose steroid, plus one or more of long-acting beta agonist, xanthine, sodium cromoglycate, anti-muscarinic.
- **Step 5 (severe)**: As in Step 4, plus oral corticosteroid.

Combination products are available as treatment often involves the prescription of both an anti-inflammatory steroid and a bronchodilator. For example, GlaxoSmithKline's Advair/Seretide unites its long-acting beta agonist Serevent with its lead steroid, Flovent/Flixotide, and has been a market leader for the last few years, with 2011 sales of almost $5bn. With the exception of the xanthines and sodium cromoglycate, both of which are small and declining classes, the main drug classes are shown on the next page.

Short- and long-acting beta agonists

These stimulate beta-2 receptors, relaxing the smooth muscles in the airways, and therefore help relieve the initial symptoms of asthma, which is the difficulty in breathing. Taken by inhalation, they do little to treat the underlying inflammation. Their main side effect comes from their absorption from the lung into the bloodstream and consequent action on beta receptors outside the lungs, causing symptoms such as tremors and palpitations.

Figure 186: Leading beta-agonist inhalers

Name	Generic	Company	Sales 2011 ($)
Short Acting			
Ventolin HFA	Albuterol	GlaxoSmithKline	$0.5bn
ProAir HFA	Albuterol	Teva	$0.4bn
Xopenex	Levabuterol	Dainippon	$0.4bn
Long Acting			
Foradil	formoterol	Novartis/Merck	$0.3bn
Serevent	salmeterol	GlaxoSmithKline	<$0.1bn

Source: Company data, Deutsche Bank, EvalautePharma

Glucocorticoids (steroids)

These products inhibit the release of the factors which cause inflammation. They have no effect on smooth muscle, however, and by inhibiting inflammation, they reduce swelling in the airways and enhance the airway's sensitivity to beta agonists. These drugs are steroids, as such, regular oral doses can produce adrenal suppression and stunt growth, particularly in children. However, inhaled steroids have very low systemic absorption and are unlikely to affect a child's growth.

Figure 187: Leading glucocorticoid inhalers

Name	Generic	Company	Sales 2011 ($)
Flixotide/Flovent	fluticasone	GlaxoSmithKline	$1.3bn
Pulmicort	budesonide	AstraZeneca	$0.8bn
QVAR	beclomethasone	Teva	$0.1bn
Asmanex	mometasone	Merck	$0.1bn

Source: Company data, Deutsche Bank, EvalautePharma

Combination products

Given the popularity of prescribing both an anti-inflammatory steroid and a long-acting bronchodilator, several products combine these two compounds into a single drug, which is given twice daily. This improves ease of administration and compliance, especially amongst children, and is used as a maintenance treatment.

Figure 188: Leading combination inhalers

Name	Generic	Company	Sales 2011* ($)
Seretide/Advair	fluticasone/ salmeterol	GlaxoSmithKline	$4.8bn
Symbicort Turbuhaler	budesonide/ formoterol	AstraZeneca	$1.6bn
Dulera	formoterol/ mometasone	Merck & Co	$0.1bn

Source: Company data, Deutsche Bank, EvalautePharma
**Sales figures are EvaluatePharma estimates of asthma share of total product sales*

Leukotriene antagonists

These products act on the inflammation cascade. Their appeal is that they act more specifically on the molecules that cause inflammation but do not have the potentially worrying side effects of steroids. However, their efficacy is modest. The leukotriene antagonists are taken orally, and because of their modest bronchodilator activity, are not used to treat bronchospasm.

Figure 189: Leading leukotriene antagonists

Name	Generic	Company	Sales 2011 ($)
Singulair	montelukast	Merck	$3.9bn

Source: Company data, Deutsche Bank, EvalautePharma

Xanthines (theophylline)

This class has long been used for bronchodilation before drug therapy by inhalers was available. However, due to the side effects associated with the xanthenes and as newer products have been developed, this category has seen its use wane.

Xolair

Xolair (omalizumab) is a humanized monoclonal antibody against IgE, and prevents IgE from binding to receptors on mast cells and other inflammatory cells, reducing the release of cytokines. It is expensive compared with other asthma medication and is used to treat an acute exacerbation in moderate to severe allergic asthma (requiring a skin prick of evidence allergy). It is not recommended for long-term use.

Clinical end-points

The two main clinical end-points used in asthma therapy are:

- **FEV1**, or the forced expiratory volume from the lungs in one second. This measures the severity of bronchospasm and extent to which it has eased following treatment.
- **PFER**, or the peak expiratory flow rate, measures the maximal flow in a forced exhalation after full inhalation in litres/minute.

Pipeline

Despite the plethora of drugs available, a significant number of asthma patients remain poorly controlled. Hence, older medications with side effects, such as xanthines, continue to be used. New drugs face a hurdle not just in demonstrating superior efficacy compared with current drugs but especially for inhaled respiratory drugs, developing the technology for delivery of the drug to the lungs. The latter factor accounts for the slow generic competition for drugs delivered in the form of dry-powder inhalers. In addition, in the US, there are no guidelines for the generic industry to work within establishing bioequivalence of inhaled steroid and long-acting asthma drugs.

Key risks to development of new LABA's reflect the FDA's concerns over an increased risk of [asthma-related] adverse events and hospitalizations in asthma patients treated with the class. The FDA will therefore continue scrutinize adverse event rates and require demonstration that the lowest effective dose has been identified. In addition, the FDA will likely scrutinize cardiac safety data due to potential pharmacological effects on the heart (i.e. heart rate/QT interval). Late-stage drugs in this category include GlaxoSmithKline/Theravance's Relovair. This is a once-daily inhaler combining fluticasone furoate and a long-acting beta agonist vilanterol and is currently in Phase III trials.

Cytokines play a key role in the development of inflammation in asthma and several interleukin (a class of cytokines) antagonist MAbs are in late stage development. Lebrikizumab, reslizumab, mepolizumab and SAR231893 are aimed at decreasing the frequency of acute exacerbations. Lebrikizumab inhibits IL-13 and suppresses secretion of periostin, which in turn activates fibroblasts involved in airway remodeling. The IL-5 antagonists, Cinquil and Bosatria, prevent binding of IL-5 to eosinophils and thus prevent eosinophil-mediated inflammation. AstraZeneca/ Kyowa Hakko Kirin's Benralizumab is a IL-5 receptor antagonist that binds to eosinophils and destroys them, depleting both, blood eosinophils as well as eosinophil precursors in the bone marrow.

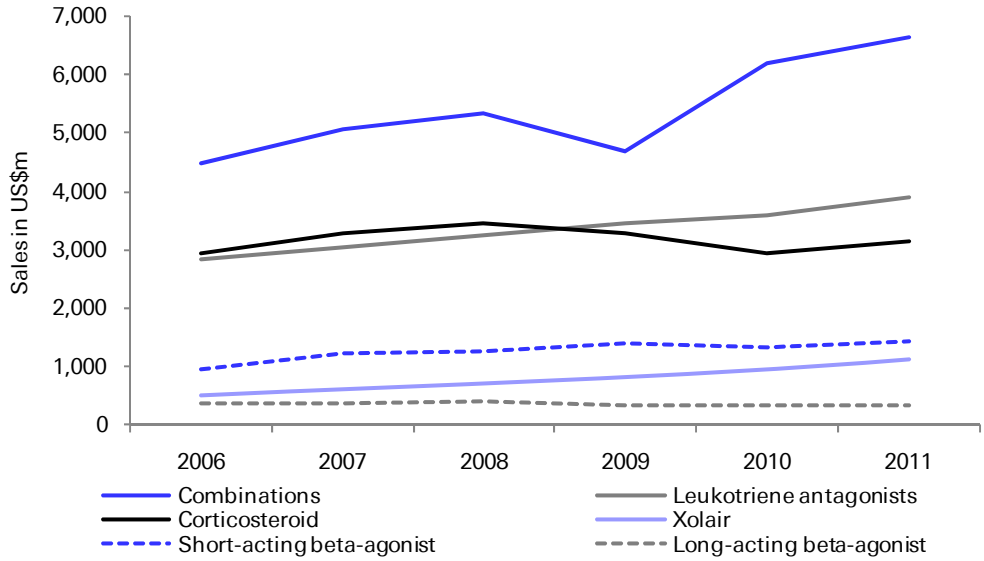
Figure 190: Selected late-stage pipeline products for asthma

Product	Generic Name	Company	Class	Stage
RG3637 (TNX-650)	lebrikizumab	Roche	Anti-IL-13 MAb	Phase III
Cinquil	reslizumab	Teva	Anti-IL-5 MAb	Phase III
Bosatria	mepolizumab	GlaxoSmithKline	Anti-IL-5 MAb	Phase III
REGN668/ SAR231893	REGN668/ SAR231893	Sanofi	Anti-IL-4 MAb	Phase II
DSP-3025	DSP-3025	Dainippon	TLR 7 agonist	Phase II
BI 1744	olodaterol	Boehringer Ingelheim	LABA	Phase III
LAS100977	N/A	Forest/Almirall	LABA	Phase II
Carmeterol	Chiesi	Chiesi	LABA	Phase II
LAS100977+ICS	LAS100977+ICS	Almirall/Forest	LABA/ICS	Phase IIa
Relovair	fluticasone & vilanterol	GlaxoSmithKline/Theravance	LABA/ICS	Phase III
Budesonide & Formoterol	budesonide & formoterol	Orion	LABA/ICS	Phase III
Fluticasone & Salmeterol	fluticasone & salmeterol	Orion	LABA/ICS	Phase III
VR315	fluticasone & salmeterol	Vectura	LABA/ICS	Phase III
Benraluzimab	Benraluzimab	AstraZeneca/ Kyowa Hakko Kirin	Anti-IL5R MAb	Phase II

Source: Company data, Deutsche Bank, EvaluatePharma

Sales

Figure 191: Sales* of asthma therapies



Source: Company data, Deutsche Bank, EvalautePharma
**Sales figures are EvaluatePharma estimates of asthma share of total product sales*

Figure 192: Sales* of asthma therapies ($ m)

Class	2006	2007	2008	2009	2010	2011
Combinations	4,489	5,073	5,325	4,685	6,186	6,626
Leukotriene antagonists	2,830	3,047	3,248	3,457	3,592	3,912
Corticosteroid	2,926	3,276	3,454	3,281	2,942	3,142
Xolair	527	612	728	820	961	1,145
Short-acting beta-agonist	971	1,248	1,255	1,410	1,341	1,431
Long-acting beta-agonist	359	384	395	348	342	334

Source: Deutsche Bank
**Sales figures are EvaluatePharma estimates of asthma share of total product sales*

Chronic obstructive pulmonary disorder

- Global sales of COPD drugs totalled c.$11bn in 2011.
- Tobacco smoke is a strong risk factor.
- National Heart, Lung, and Blood Institute estimates prevalence is decreasing in the US.
- COPD accounts for 5% of global deaths, 90% of them in low and middle income countries.

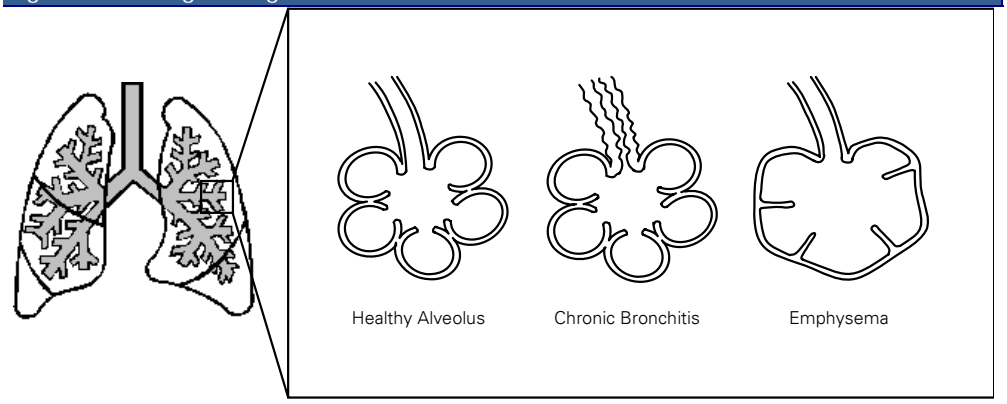
Chronic Obstructive Pulmonary Disorder (COPD) is a broad term covering several closely related respiratory diseases, including chronic bronchitis and emphysema. It is estimated to affect 5% of the population and is the fourth-leading cause of death globally. Cigarette smoking is the primary cause of COPD, responsible for 80-90% of all cases. While the prevalence of smoking has decreased in recent years, COPD is on the rise. This is explained by the fact that COPD develops only after many years of smoking. Hence, we are now seeing the effects of changes in smoking demographics from decades ago.

Physiology

Both chronic bronchitis and emphysema are considered part of COPD and many patients have elements of both. However, they have different symptoms and pathology. Chronic bronchitis is associated with chronic coughing and excess mucus secretion in the bronchial tree ('chronic' is defined as occurring on most days for at least three months of the year and recurring over the course of at least two consecutive years). This is caused by prolonged exposure to bronchial irritants, chronic bronchitis results in inflammation and narrowing of the airways. Emphysema, on the other hand, is characterised by enlargement of the air sacs that lie at the ends of the bronchial branches in the lungs. Due to repetitive irritation, the normally elastic air sacs, called alveoli, become rigid and the walls of the airways are destroyed. This tissue damage reduces the surface area in the sacs available for gas exchange, resulting in a diminished surface area for oxygen exchange.

These two conditions can be considered at opposite ends of the spectrum of disease, and most sufferers exhibit symptoms of both conditions, with one or the other predominating. Figure 193 emphasises the difference between them.

Figure 193: Lung damage in COPD



Source: Deutsche Bank

Damage to the alveoli occurs due to destruction of elastin, a protein responsible for maintaining the strength of the alveolar walls. Smoking facilitates this process by stimulating production of elastase, a protein that breaks down elastin. There is also a rare hereditary condition, known as "familial emphysema," that is characterised by genetic deficiency of α1-antitrypsin (AAT). Because AAT normally inhibits the destructive effects of elastase, deficiency of this protein can lead to emphysema in otherwise low-risk non-smokers.

Pharmacological treatment

Despite the physiological differences between COPD and asthma, drug therapies for COPD have similar aims – to relax and open narrowed airways, to reduce inflammation, and to loosen built-up mucus. The three primary groups of drugs are described below. (Also see the previous section on asthma).

Beta agonists (both short and long-acting)

Similar to their use in asthma, these drugs facilitate bronchodilation by stimulating beta 2 receptors to cause relaxation of the smooth muscle around the airways. They generally have a rapid onset of action (5-30 mins) and are classified as either short-acting (SABA; i.e. albuterol/ventolin) or long-acting (LABA; salmeterol/formoterol). Salmeterol has been shown to improve lung function and reduce COPD exacerbations. However, it does not have the latter claim in its label. It has a slower onset of action (c.20-30mins) than the competing LABA formoterol (c.5 mins; Foradil).

Figure 194: Leading Long-acting beta-agonists

Brand	Generic	Company	Sales* 2011 ($)
Serevent	salmeterol	GlaxoSmithKline	$0.3bn
Brovana	arformoterol	Dainippon	$0.1bn
Arcapta	indacaterol	Novartis	$0.1bn

Source: Company data, Deutsche Bank, EvalautePharma
**Sales figures are EvaluatePharma estimates of COPD share of total product sales*

Anticholinergics

Anticholinergic drugs are also used as a first-line therapy and open up the airways in a different way to beta-agonists. They block the action of the neurotransmitter acetylcholine by antagonizing the muscarinic receptor (hence they are known as muscarinic antagonists) in the smooth muscle of the bronchial tree. There are currently both short-acting drugs (known as SAMAs) such as ipratropium (Atrovent) which work for about 8 hours and long-acting drugs (i.e. long-acting muscarinic antagonists or

LAMAs) such as tiotropium (Spiriva), which has a 24 hour duration of action. The main side effect of SAMAs and LAMAs is dry mouth. Spiriva has been shown to improve lung function, reduce breathlessness and improve exercise capacity and quality of life. In addition it has been shown to be superior to the LABA salmeterol in reducing exacerbations. New once and twice-daily LAMA's from Novartis (Seebri Breezehaler; NVA237) and Forest/Almirall (Eklira/Tudorza) have recently been approved by the EMA and FDA/EMA respectively.

Figure 195: Leading anti-cholinergic inhalers

Brand	Generic	Company	Sales 2011 ($)
Spiriva	Tiotropium	Boehringer Ingelheim	$4.4bn
Atrovent	ipratropium bromide	Boehringer Ingelheim	$0.4bn

Source: Company data, Deutsche Bank, EvalautePharma

Inhaled corticosteroids (ICS)

Unlike anticholinergics and beta agonists, steroids have no direct effect on dilating the airways. The effects of ICS drugs are to target the inflammatory response by inhibiting the release of factors that cause inflammation, hence reducing the incidence of acute exacerbations. However, the benefits of ICS therapy in COPD are a matter of debate. ICS monotherapy treatment has little effect in COPD and regular ICS treatment does not affect the decline of the disease. Treatment has however been shown to reduce the rate of exacerbations when used in combination with LABA (LABA/ICS) and improve lung function. However, this is associated with an increased risk of pneumonia and most significant benefit is only seen in a subgroup of patients.

Phosphodiesterase inhibitors

The non-specific oral phosphodiesterase inhibitor theophylline has bronchodilatory effects but is only used in patients with persistent symptoms due to toxicity. More recently the selective PDE-IV inhibitor Daxas/Daliresp (roflumilast) has been approved for severe patients. However, its efficacy is modest and it is associated with gastrointestinal side effects.

Fixed-dose combinations

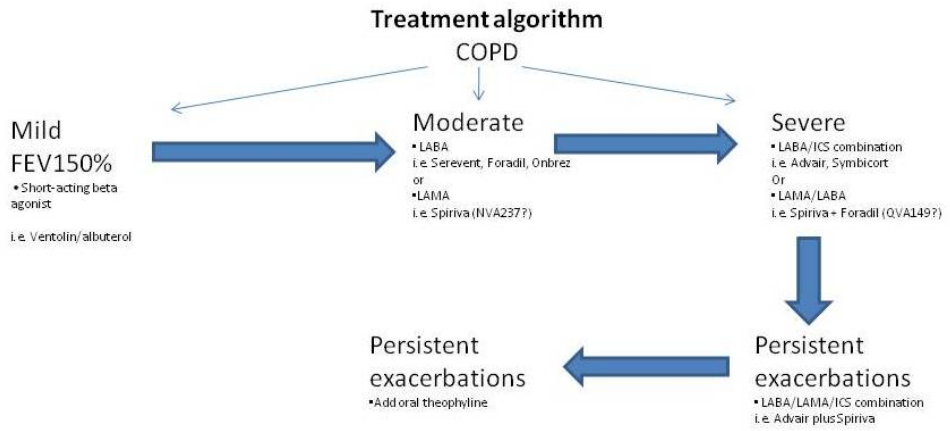
As with asthma, combination products command the largest share of the COPD market, improving the ease of administration and compliance. Most studies exploring combination therapy have demonstrated benefits over single-agent treatment. As such COPD management generally consists of escalating combination therapy. Recent data has also supported efficacy of triple combination therapy LAMA+LABA+ICS vs LABA+ICS alone. Fixed-dose combinations of various drugs have been developed to help improve compliance and improve outcomes. Advair is currently the most commonly prescribed combination treatment for COPD. It is a combination of the LABA salmeterol and the ICS fluticasone. A combination of the LAMA ipratropium is available with a short-acting beta agonist. However, sales are modest as ipratropium is seen as an inferior drug to Spiriva and the beta agonist provides only short acting bronchodilation.

Figure 196: Leading combination inhalers for COPD

Brand	Generic	Company	Sales* 2011 ($)
Seretide/Advair	fluticasone/ salmeterol	GlaxoSmithKline	$3.3bn
Symbicort Turbuhaler	budesonide/ formoterol	AstraZeneca	$1.5bn
Combivent	albuterol/ ipratropium	Boehringer Ingelheim	$0.2bn

Source: Company data, Deutsche Bank, EvalautePharma
**Sales figures are EvaluatePharma estimates of COPD share of total product sales*

Figure 197: COPD treatment algorithm



Source: Deutsche Bank

Clinical end-points

Among the tools used to measure the severity of COPD is forced expiratory volume (FEV1). FEV1 provides an indication of airway obstruction by measuring the volume of air a patient is able to exhale in one second. Although FEV1 decreases with age in healthy adults, this decline is two to three times more pronounced in patients with COPD. Consequently, an improvement in FEV1 versus placebo generally serves as a key end-point in clinical studies. In addition to drugs treating the underlying disease, an improvement in exacerbations is sought.

Pipeline products

The size and growth potential of the COPD market have encouraged companies to develop new treatments. The vast majority of products in late stage development for COPD are LAMAs or LABAs. They each have additional potential benefits such as lower side effects (NVA237) or better efficacy (Arcapta/QVA149), require less frequent dosing (i.e. once-daily) (QVA149, Relovair, QMF149) or provide novel combinations in handy fixed-dose devices (QVA149, Relovair, QMF149). Although the latter may seem like simply one of convenience which would make pricing negotiations tricky, we believe the benefits of less frequent dosing on compliance and potentially clinical outcomes in both asthma and COPD is well recognized by physicians. We expect companies to utilize data from Phase III trials to develop pharmaco-economic arguments to support pricing such as improvements in quality-of-life and lower frequency of exacerbations. As such we believe once-daily therapies will be perceived as a meaningful advance and should take significant market share.

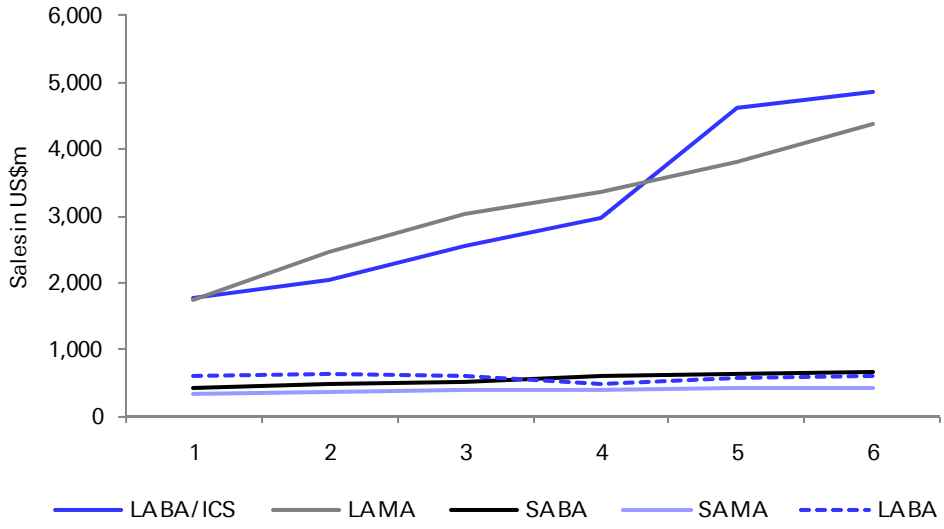
Figure 198: Selected late-stage pipeline products for COPD

Product	Generic Name	Company	Class	Stage
BI 1744	olodaterol	Boehringer Ingelheim	LABA	Phase III
LAS100977	N/A	Forest/Almirall	LABA	Phase II
Carmoterol	Carmoterol	Chiesi	LABA	Phase II
NVA237	glycopyrrolate	Novartis	LAMA	Phase III (US)
GSK961081	GSK961081	GSK/Theravance	MABA	Phase II
Mucodyne	carbocysteine	Kyorin Holdings	Mucolytic	Phase III
Erdosteine	erdosteine	iNova Pharmaceuticals	Mucolytic	Phase III
Relovair	fluticasone & vilanterol	GlaxoSmithKline/Theravance	LABA/ICS	Phase III
Budesonide & Formoterol	budesonide & formoterol	Orion	LABA/ICS	Phase III
VR315	fluticasone & salmeterol	Vectura	LABA/ICS	Phase III
LAS100977+ICS	LAS100977+ICS	Almirall/Forest	LABA/ICS	Phase IIa
QVA149	glycopyrrolate & indacaterol	Novartis	LAMA/LABA	Phase III
GSK573719/ vilanterol ('719/VI)	N/A	GlaxoSmithKline	LAMA/LABA	Phase III
Tiotropium/ olodaterol	tiotropium & olodaterol	Boehringer Ingelheim	LAMA/LABA	Phase III
Aclidinium & formoterol	Aclidinium & formoterol	Almirall/Forest	LAMA/LABA	Phase II

Source: Company data, Deutsche Bank, EvalautePharma

Sales

Figure 199: Sales of COPD therapies ($ m)



Source: Company data, Deutsche Bank, EvalautePharma
**Sales figures are EvaluatePharma estimates of COPD share of total product sales*

Figure 200: Sales of COPD therapies ($ m)

Class	2006	2007	2008	2009	2010	2011
Beta agonist/ Corticosteroid	1,782	2,061	2,568	2,970	4,631	4,851
Long-acting muscarinic antagonist (LAMA)	1,735	2,457	3,042	3,351	3,799	4,389
Short-acting beta agonist	418	500	530	621	637	661
Short-acting muscarinic antagonist	330	371	409	399	420	428
Long-acting beta agonist (LABA)	613	631	614	492	564	609

Source: Company data, Deutsche Bank, EvalautePharma
**Sales figures are EvaluatePharma estimates of COPD share of total product sales*

Allergic rhinitis

- Sales of drugs for allergic rhinitis totalled almost $9bn in 2011.
- Around 10% to 30% people worldwide are affected by allergic rhinitis, with incidence varying across geographies.
- Leading products include Singulair (Merck), Nasonex (Merck) and Allegra (Sanofi).

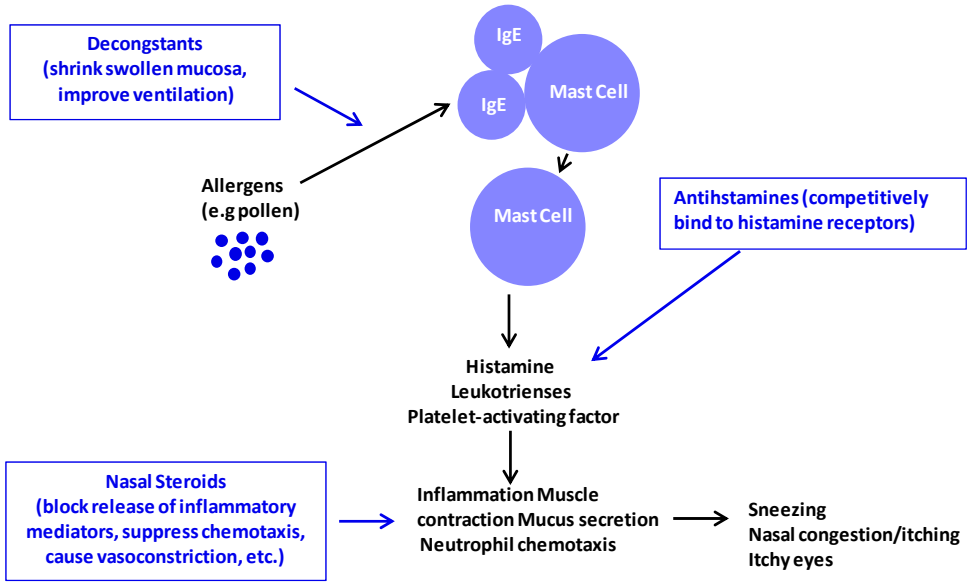
Allergic rhinitis results from the body's hypersensitivity to normally innocuous particles which, when inhaled through the nose, elicit an adverse reaction. Allergic rhinitis may either be seasonal or perennial. Seasonal allergies, known as hay fever, arise following exposure to seasonal allergens (primarily pollens) that are present during spring and/or autumn. Perennial allergic rhinitis is present year-round and is caused by non-seasonal allergens such as dust mites, animal hair, or skin particles and moulds. Allergic rhinitis is responsible for more than 13 million physician office visits in US each year.

Physiology

Allergic rhinitis is triggered by exposure to normally innocuous substances that elicit an adverse immune reaction. There is strong evidence of a genetic component to the disease, with children of one allergic parent having a 30% risk of developing allergic rhinitis and children of two allergic parents having a risk of almost 50%. Allergen exposure is an additional predisposing factor, because in order to develop allergies, one must have had an initial exposure to the allergen. Therefore, many potential allergy sufferers may never develop symptoms because they have never come into contact with the offending allergen.

Allergies are caused by an antibody-mediated immune reaction to specific allergens. Following initial exposure, allergen-specific IgE antibodies are produced that bind to certain immune cells, called mast cells, located in the nasal passage. Upon re-exposure, the mast cell-bound IgE molecules interact with the airborne antigen, triggering the release of inflammatory mediators such as histamine, leukotrienes, and platelet-activating factor (PAF) as shown in Figure 201. These agents are responsible for the acute inflammatory response, along with increased mucus secretion, muscle contraction, and other allergic symptoms. A further late-stage reaction may also occur in some patients hours after the initial exposure, where inflammatory cells, such as eosinophils, monocytes, and macrophages, cause sustained symptoms despite the absence of the original allergen.

Figure 201: Early-phase allergic reaction



Source: Dipiro, Talbert, Yee, Matzke, Wells and Posey, Deutsche Bank

Pharmacological treatment

Although avoidance of the relevant allergens is the most direct method to prevent allergic rhinitis, not surprisingly, it is usually the most difficult, given the widespread prevalence of many seasonal and perennial antigens. Immunotherapy, in which a patient undergoes repeated exposure to the allergen in an attempt to desensitise his or her immune system, may offer long-term benefit, but its use is also limited, given the significant expense, time commitment, and potential risks involved.

Thus, treatment of allergic rhinitis primarily relies on pharmacological therapies, namely antihistamines, decongestants, and steroids. Antihistamines are histamine receptor antagonists that competitively bind to H1 histamine receptors, thereby inhibiting histamine-induced inflammation. Because antihistamines are better at preventing the actions of histamine rather than reversing the effects once they have taken place, they are best given prior to the anticipated allergen exposure. Many of the first-generation drugs such as diphenhydramine HCl (Benadryl) and clemastine fumerate (Tavist) have long been available over the counter (OTC). While offering a therapeutic benefit, drowsiness is often a chief complaint of patients taking these drugs. In addition, several first-generation drugs are associated with drug-drug interactions, a key factor that led to the withdrawal of Hoechst Marion Roussel's Seldane and J&J's Hismanal.

Given the side effect profile of the first-generation antihistamines, second generation drugs have largely taken over the prescription market. Although all drugs in this class are marketed as non-sedating, Zyrtec exhibits a higher sedation rate than the earlier compounds, terfenadine and astemizole.

Growth in the allergy and allergic rhinitis segment in recent years has been led Merck's franchise: Singulair, Clarinex and Nasonex. Apart from these, the past decade has seen expiry of key drugs for the ailment - Allegra/Telfast in 2005 and Zyrtec in 2007. Several drugs are now available over the counter or are about to lose patent protection, including Singulair (2012) and Nasonex.(2014). With very few new allergy drugs in the pipeline, it appears probable that this sector will continue its trend of genericisation.

Figure 202: Leading prescription antihistamines for allergic rhinitis

Name	Generic	Company	2011 sales ($)
Allegra	fexofenadine	Sanofi	$0.8bn
Clarinex	desloratadine	Merck & Co	$0.6bn
Claritin OTC	loratadine	Merck & Co	$0.5bn
Allelock	olopatadine	Kyowa Hakko Kirin	$0.4bn
Zyrtec	cetirizine	UCB	$0.3bn
Claritin Rx	loratadine	Merck & Co	$0.3bn
Zyrtec OTC	cetirizine	Johnson & Johnson	$0.3bn

Source: Company data, Deutsche Bank, EvalautePharma

Given the nasal congestion often associated with allergic rhinitis, many patients also take a topical or systemic decongestant. Topical decongestants, available as drips or sprays, are highly effective and available OTC, contributing to their widespread use. While not as effective in terms of immediate onset of action, oral decongestants may last longer and cause less local irritation. In addition, Merck, Sanofi, and UCB (the makers of Claritin, Allegra, and Zyrtec, respectively) have all developed combined antihistamine/decongestant products, designated with a "D" (e.g., Claritin D), in an effort to provide added convenience to consumers.

Nasal steroids offer an added mode of treatment, particularly for patients who suffer from perennial rhinitis. These drugs, given as an intranasal spray, are most effective when administered ahead of exposure to allergens. Therefore, they are administered daily, with therapeutic benefits becoming evident two to three weeks later.

Figure 203: Leading nasal steroids for allergic rhinitis

Name	Generic	Company	2011 sales ($)
Nasonex	mometasone	Merck	$1.3bn
Avamys/Veramyst	fluticasone furoate	GlaxoSmithKline	$0.4bn
Flixonase/Flonase	fluticasone propionate	GlaxoSmithKline	$0.2bn
Rhinocort	budesonide	AstraZeneca	$0.2bn
Nasacort	triamcinolone	Sanofi	$0.1bn

Source: Company data, Deutsche Bank, EvalautePharma

Merck's Singulair (montelukast), originally developed for asthma, is also approved for seasonal allergic rhinitis. Singulair acts through its mechanism of action as a leukotriene antagonist to reduce nasal oedema and secretions. $1.6bn of 2011 sales were attributed to this indication.

Pipeline products

One interesting mode of action which Merck and ALK-Abello are exploring is in the area of sublingual immunotherapy. By regularly exposing the body to the allergen, it aims to desensitize the body to the allergen, therefore reducing the allergic response. A grass pollen immunotherapy vaccine is approved in Europe and in Phase III studies in US. Merck recently presented positive Phase III data on a ragweed immunotherapy vaccine. ALK is also studying tablet vaccines against house dust mites, tree pollen and cats.

Another mechanism being targeted is the blocking of prostaglandin D2 by CRTH2 antagonists, which inhibits the exacerbation of the allergic inflammation process. Novartis' QAV680 and Oxagen's OC000459 are currently in Phase II clinical studies while Actelion's CRTH2 follow-up drug is in Phase I studies. Actelion recently

terminated development of setipiprant, the first oral CRTH2 antagonist, due to lack of demonstrable efficacy in late stage trials.

Figure 204: Selected late-stage pipeline products for allergic rhinitis

Name	Company	Class	Status
MK-7243	Merck	Grass Allergy Immunotherapy	Phase III
MK-3641	Merck	Ragweed Allergy Immunotherapy	Phase III
QAV680	Novartis	CRTH2 receptor antagonist	Phase II
OC000459	Oxagen	CRTH2 receptor antagonist	Phase II
CRTH2 antagonist follow up	Actelion	CRTH2 receptor antagonist	Phase I

Source: Deutsche Bank, Company data

Osteoporosis

- Sales of drugs for osteoporosis totalled over $8bn in 2011.
- More than 75 million people globally suffer from osteoporosis, 80% of whom are women.
- Key products include Amgen's Prolia, Novartis' Aclasta, P&G/Sanofi's Actonel, Merck's Fosamax, and Eli Lilly's Forteo.

Osteoporosis (literally "porous bone") is a disease in which bones gradually become porous and consequently weaker and increasingly brittle. Osteoporosis is believed to affect 10 million people in the US alone and another 34 million are believed to be at risk of it due to low bone mineral density. The disease is age-related and most common in women above the age of 50 (post-menopausal osteoporosis, or PMO). It is defined as a bone mineral density (BMD) that is more than 2.5 standard deviations lower than that of a young adult (T-score on BMD < -2.5). A common complication of osteoporosis is bone fractures as a result of falls, which most commonly affect the hip, spine, and wrist. Of these, hip fractures have the most severe impact, with about half of these patients not being able to walk without assistance subsequently, and 20% dying within one year as a result of medical complications. In addition, recent research has highlighted the importance of non-hip and non-spine fractures such as wrist/hand, arm/shoulder, pelvis, rib and leg, which although less serious require significantly greater healthcare resources given their 5-fold greater incidence. In the US, it is estimated that two million men and eight million women over the age of 50 have osteoporosis, while an additional 14 million have osteopenia.

With life spans increasing and the elderly representing a greater proportion of the population, the financial burden of treating the disease is increasing. In addition, adherence to chronic treatment is poor and remains a major hurdle, especially when treatment is preventative. Studies have indicated that 50%-75% of women who initiate any osteoporosis therapy are not on therapy 12 months post initiation. Consequently, there is demand for better medications to reduce the risk of osteoporosis-related complications (albeit, hurdles are high, given the availability of low-cost generics).

Physiology

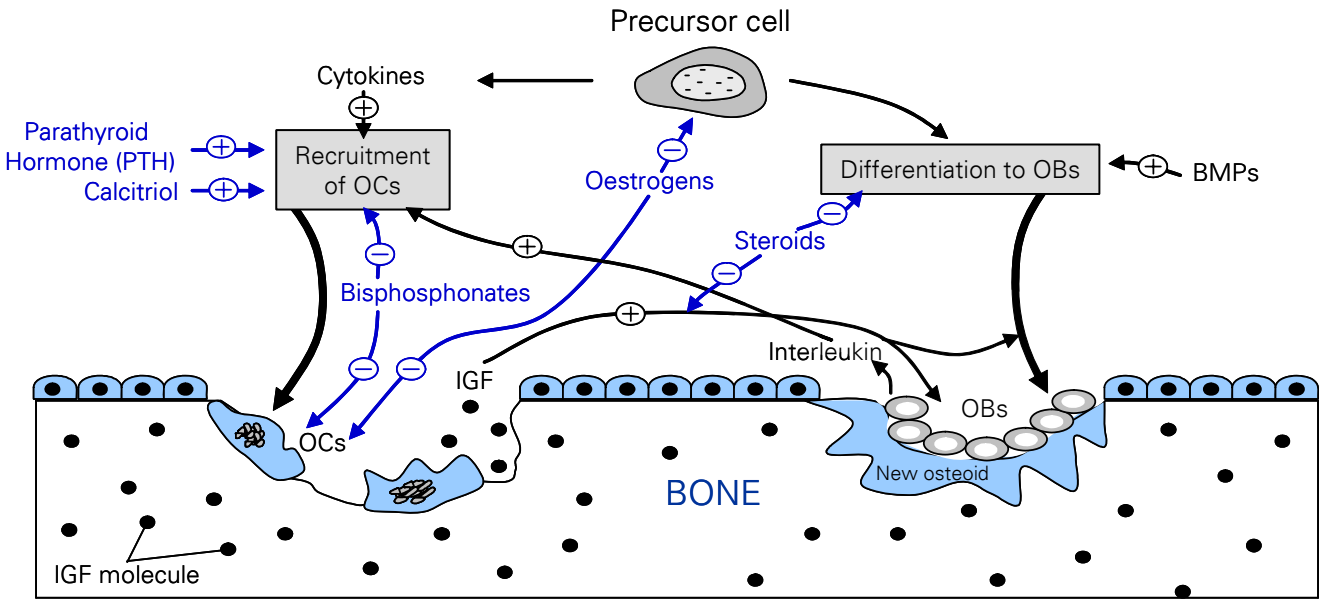
Bone is predominantly comprised of collagen, calcium, and phosphate ions, bound together by phosphoproteins. Bone is created by the formation of osteoid (a protein-rich mixture), onto which calcium phosphate crystals are deposited (as calcium hydroxylapatite), so establishing a hard bone matrix. In healthy adults, the bone mass is continuously being remodelled, with some bone being resorbed and some new bone laid down. This runs contrary to popular belief that adult bones are constant. The process of remodelling is undertaken by two types of cells – osteoblasts, which secrete new bone matrix, and osteoclasts, which break it down – and is closely regulated by the action of hormones (including oestrogen, which dampens the activity of the osteoclasts) and other chemicals.

The process of bone remodelling is dynamic, although bone breakdown can be also initiated when bone is damaged or when plasma calcium falls below a particular level. Key to the process is the parathyroid gland (a hormone secreting gland in the neck) in maintaining plasma calcium concentrations. Receptors on the parathyroid cells react to a decline in the calcium concentration, triggering the secretion of parathyroid hormone

(PTH), which then acts on a number of pathways. One of these pathways involves the breakdown of bone, where PTH:

- Promotes the formation of the hormone calcitriol from vitamin D, which facilitates the formation of osteoclasts from precursor cells;
- Encourages the action of chemical messengers or cytokines to stimulate osteoclastic activity. The osteoclasts then secrete hydrogen ions and proteolytic (protein-cleaving) enzymes that break down bone and release its components, such as calcium and insulin-like growth factor (IGF1) from the site of their action.

Figure 205: Bone remodelling process



Source: Rang, Dale & Ritter, Deutsche Bank

IGF1 then stimulates the activation and formation of osteoblasts. Once activated, the osteoblasts migrate to the site of bone breakdown, and, together with collagen-producing cells (called chondrocytes), produce the osteoid matrix in which the crystals of calcium phosphate are deposited to create new bone. In addition, the osteoblasts release interleukins that activate the osteoclast cells, so reinitiating the remodelling cycle.

Although the cycle is dynamic, there are several important regulatory mechanisms. These tend to regulate osteoclast activity.

- Increased plasma calcium concentration acts on receptors on the surface of the parathyroid cells and inhibit PTH secretion, thereby preventing further formation of osteoclasts.
- Oestrogen acts to inhibit the action of the interleukins that stimulate osteoclast activity, inhibiting the development of osteoclast precursor cells, and encourages the osteoclasts to undergo programmed cell death (apoptosis). Thus, the decline of oestrogen in post-menopausal women leads to an increased incidence of osteoporosis.
- Calcium levels also have an impact on the activity of the hormone, calcitonin, with a rise in calcium concentration leading to an increase in calcitonin release.

Calcitonin is secreted by the special 'C' cells in the thyroid. This binds to a receptor on osteoclasts, and stops further breakdown of the bone.

Osteoporosis is commonly found in:

- Post-menopausal women, whose oestrogen levels have fallen to the extent that control of the inhibition of osteoclast activation is reduced, and
- Elderly men and women, whose bodies fail to rebuild bone that has been broken down as a result of age-related factors, such as a reduction in osteoblast activity and calcium uptake.

Importantly, because excessive levels of steroids tend to inhibit the formation of osteoblasts and their activation, osteoporosis can also arise as a side effect of excessive use of steroids (glucocorticoids) in controlling inflammatory disease in young people.

Pharmacological treatment

There are currently two major classes of compounds on the market for treating and preventing osteoporosis: bisphosphonates and selective oestrogen receptor modulators (SERMs). Other alternatives include oestrogen or hormone replacement therapies (which are largely used for prevention), parathyroid hormone and calcitonins.

Figure 206: Bisphosphonates vs. SERMs

	Bisphosphonates	SERMs
Sales 2011 ($)	$3.9bn	$1.4bn
Leading product	Actonel (Warner Chilcott/ Sanofi)	Evista (Eli Lilly)
Point of action	Inhibits osteoclast and promotes osteoclast apoptosis (death)	Inhibits osteoclast
First Fracture reduction	47%	55%

Source: Company data, Deutsche Bank, EvaluatePharma

Bisphosphonates

Bisphosphonates currently have by far the largest volume share in the osteoporosis market. Bisphosphonates are the treatment of choice because of their: 1) long safety record; 2) high affinity for bone; 3) oral convenience; 4) applicability across a broad spectrum of osteoporosis types (post-menopausal, male, steroid induced osteoporosis as well as Paget's disease); and 5) low price. They work by inhibiting the activation of cells called osteoclasts and promoting their death (by apoptosis). This slows bone breakdown and reduces the risk of fractures. They have proven to be highly effective in slowing bone breakdown and have found an additional use in the palliative treatment of bone metastases (cancer that has spread to the bone) to prevent fractures. For example, Novartis' Aclasta/Reclast used for osteoporosis is identical to Zometa and has been branded differently for the treatment of bone metastases.

The main side effect of bisphosphonates is gastrointestinal complaints, e.g., stomach ulcers. This has lead to the prescribed ritual of taking them 30 minutes before a meal with a full glass of water, after which time patients must remain in an upright position. In an effort to minimise this inconvenience, newer formulations of bisphosphonates have moved from once-daily to once-weekly dosing. Fosamax, the previous leading blockbuster in this class with more than $3bn in peak sales, went generic in 2008. Boniva lost patent protection in 2012 and Aclasta could follow in 2013. Consequently, sales in this class are set to decline further.

Figure 207: Leading bisphosphonates

Name	Generic	Company	2011 sales ($)
Actonel	risedronate	Warner Chilcott/ Sanofi	$1.1bn
Fosamax	alendronate	Merck	$0.8bn
Boniva	ibandronate	Roche	$0.8bn
Reclast	zoledronic acid	Novartis	$0.6bn
Bonalon	alendronate	Teijin	$0.3bn

Source: Company data, Deutsche Bank, EvaluatePharma

Selective oestrogen receptor modulators (SERMs)

There is only one SERM currently approved by the FDA, Eli Lilly's Evista. This drug mimics the action of oestrogen by binding to specific oestrogen receptors on osteoclasts, slowing the rate of bone loss. It benefits from oral dosing and is modestly effective at improving bone mineral density and reduces the risk of vertebral fractures. In addition, Evista received approval from the FDA in 2007 for use in reducing the risk of breast cancer in postmenopausal women with high risk or with osteoporosis. However, it is associated with side effects including hot flashes, edema, and increased risk for venous thromboembolic events (VTEs) and fatal strokes. In addition, Pfizer has a drug of the SERM class marketed as Conbriza (bazedoxifene). It is approved by the EMA for the reduction in spine fractures (but not hip) but not the FDA.

Figure 208: Leading SERMs

Name	Generic	Company	2011 sales ($)
Evista	raloxifene	Eli Lilly	$1.4bn

Source: Company data, Deutsche Bank, EvaluatePharma

Parathyroid hormone

Eli Lilly's Forteo is a recombinant parathyroid hormone, initially approved by the FDA in 2002. It is an analogue of parathyroid hormone, daily stimulation with which results in preferential stimulation osteoblastic activity over osteoclastic activity. Hence, Forteo works by not only slowing bone breakdown but by actually increasing bone formation (it is a "bone builder"). However, due to the proliferative property, duration of treatment is restricted and it has a black box warning against osteosarcoma. Despite this, sales have climbed to c.$1bn.

Figure 209: Recombinant parathyroid hormone

Name	Generic	Company	2011 sales ($)
Forteo	teriparatide recombinant human	Eli Lilly	$0.9bn

Source: Deutsche Bank

Anti-RANKL MAb

Amgen/GlaxoSmithKline's Prolia (denosumab) is a fully human monoclonal antibody which inhibits RANKL (Receptor Activator for Nuclear Factor kB Ligand), a regulator which stimulates maturation of osteoclasts, and in so doing reduces osteoclastic activity and bone resorption. It is approved for the treatment (but not prevention) of postmenopausal osteoporosis patients at high risk for fracture, to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for non-metastatic prostate cancer and for treatment to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. It is also approved under the brand Xgeva for the prevention of skeletal-related events in cancer patients. It is dosed subcutaneously every six months.

Pipeline products

No specific class of drugs dominates the pipeline for osteoporosis treatment and a number of novel treatment methods are being investigated. Merck's odanacatib selectively inhibits cathepsin-K, the enzyme in osteoclasts responsible for breakdown of existing bone. A phase II trial was halted early due to robust efficacy and a favorable risk-benefit profile. UCB/ Amgen's CDP7851 (romosozumab) is an anti-sclerostin MAb that increases bone density by targeting sclerostin, a protein that inhibits osteoblast activity. The drug met its primary endpoint in phase II trials by significantly increasing lumbar spine bone density vs placebo. Eli Lilly, phase II pipeline drug, blosozumab, also targets sclerostin. Pfizer has filed for approval of Aprela, a combination of bazedoxifene and conjugated estrogens, for treatment of post-menopausal symptoms.

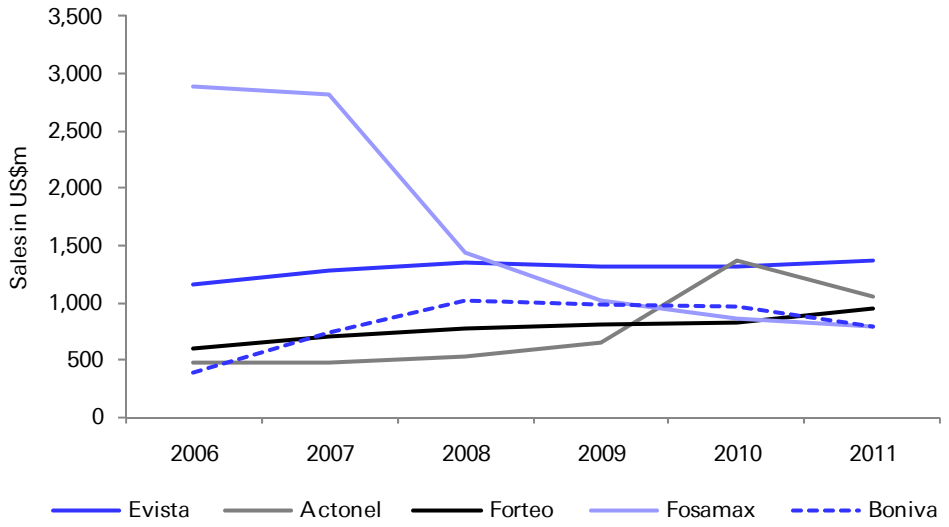
Figure 210: Selected late-stage pipeline products for osteoporosis

Name	Generic	Company	Stage
CDP7851/ AMG 785	romosozumab	Amgen/ UCB	Phase III
Aprela	bazedoxifene/conjugated estrogen	Pfizer	Phase III
MK-0822	odanacatib	Merck	Phase III
Femivia	Acolbifene/ prasterone	EndoCeutics	Phase III
LY2541546	blosozumab	Eli Lilly	Phase II

Source: Deutsche Bank

Sales

Figure 211: Sales of leading osteoporosis drugs



Source: Company data, Deutsche Bank, EvaluatePharma

Figure 212: Sales of leading osteoporosis drugs ($ m)

Brand	Company	2006	2007	2008	2009	2010	2011
Evista	Eli Lilly	1161	1272	1355	1321	1315	1370
Actonel	Warner Chilcott/ Sanofi	471	477	533	652	1364	1055
Forteo	Eli Lilly	594	709	779	817	830	950
Fosamax	Merck	2893	2814	1433	1015	855	789
Boniva	Roche	390	740	1025	977	974	787

Source: Company data, Deutsche Bank, EvaluatePharma

Pain

- Sales of pain-related medication exceeded $15bn in 2011.
- Growth of the category is undermined by generic competition and controversy surrounding COX-2 inhibitors.
- Treatment is based on severity, and the acute versus the chronic nature of condition.

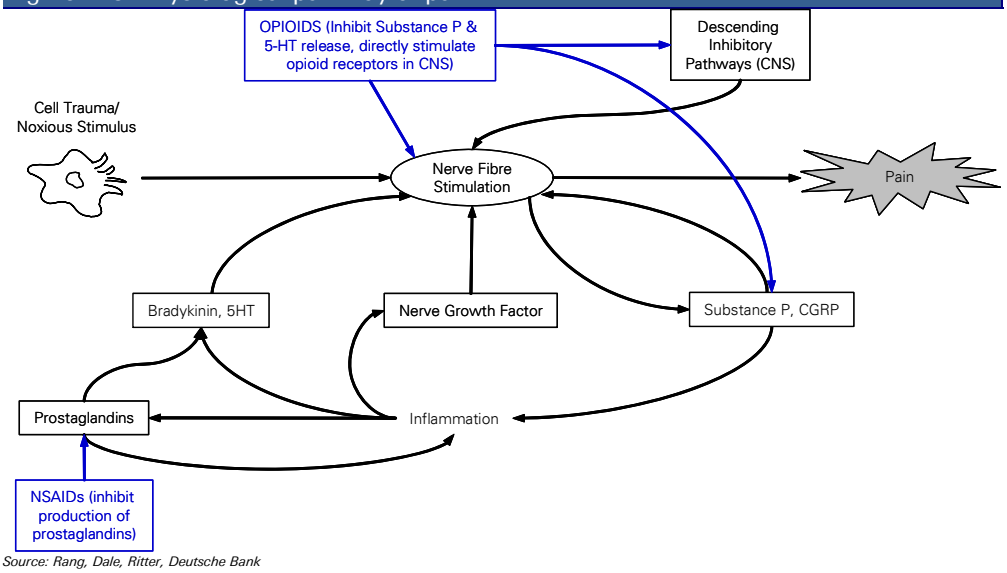
Pain is a common symptom and serves a protective function in most day-to-day situations. However, it is also associated with many medical conditions, adding to the discomfort and unhappiness of the sick patient. Hence, the pain market is one of the world's largest and most rapidly growing markets. According to a National Pain Survey conducted in the US, over 25 million people in the US suffer from acute pain related to injury or surgery, and another 50 million experience chronic pain.

Physiology

Pain is classified into several categories to help determine the appropriate treatment. First, it is broadly characterised as acute or chronic. Acute pain is short-lived, whereas chronic pain is usually described as persisting for more than three to six months.

Most painful sensations are a result of the nociceptive pathway. Following injury, damaged cells release several chemical mediators, including bradykinin, 5-hydroxytryptamine (5-HT) and histamine. Histamine primarily initiates an inflammatory response. Bradykinin and 5-HT stimulate pain receptors, called nociceptors, which pass the signal from the peripheral nerves to the spinal cord and brain, leading to the sensation of pain. In addition, at the time of cell injury, arachidonic acid is released, which is converted via the enzyme cyclooxygenase, to prostaglandins. While not stimulating pain directly, these molecules enhance the pain-producing effects of bradykinin and 5-HT and contribute to the inflammatory response.

Figure 213: Physiological pathway of pain



Source: Rang, Dale, Ritter, Deutsche Bank

Pharmacological treatment

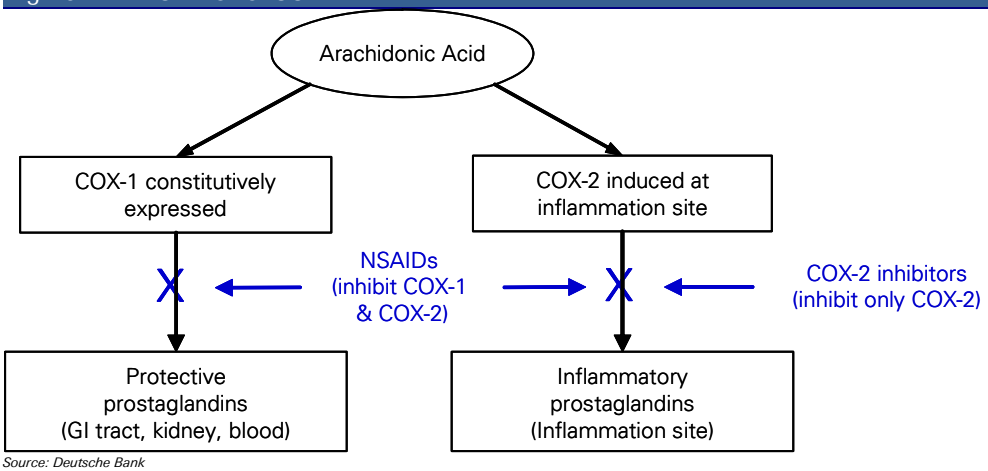
Given the complex causes and manifestations of pain, treatments vary widely and are best categorised into several groups based on the relevant conditions they aim to treat.

Mild-to-moderate pain (e.g., headache, arthritis)

Low-level pain is generally treated with aspirin, paracetamol, ibuprofen, or other non-steroidal anti-inflammatory drugs (NSAIDs). There are currently more than 50 different NSAIDs on the market, most of which differ slightly in pharmacological characteristics or side effect profile but all of which (with the exception of paracetamol) inhibit the inflammatory reaction. The NSAIDs target the cyclooxygenase (COX) enzyme, which is responsible for the production of prostaglandins. There are two types of cyclooxygenase. The first of these, COX-1, exhibits protective effects and is expressed in most tissues, including the kidneys, gastrointestinal tract and blood platelets, while the second form of the enzyme, COX-2, is involved in the inflammatory pathway.

As most NSAIDs do not discriminate between these two enzymes, they disrupt the protective efforts of COX-1, leading to unwanted side effects such as gastrointestinal and kidney irritation. In an effort to reduce these complications, COX-2 inhibitors were developed which selectively target the COX-2 enzyme. Although applicable in a number of pain indications, the COX-2 inhibitors have been most widely used for the treatment of osteoarthritis, a painful condition caused by erosion of cartilage and bone in the joints. Osteoarthritis is estimated to affect more than 50% of people over 65 years old and nearly everyone over the age of 75. As the elderly are also more susceptible to NSAID-associated gastritis, COX-2 inhibitors have an established benefit in this category of patients.

Figure 214: NSAIDs vs. COX-2



Source: Deutsche Bank

In late September 2004, Merck announced the worldwide withdrawal of its blockbuster COX-2 inhibitor, Vioxx. This was based on data from a three-year trial designed to evaluate the use of Vioxx in preventing the recurrence of colorectal polyps, which showed that patients receiving Vioxx had a twofold greater risk of cardiovascular events (e.g., stroke or heart attack) compared with those receiving placebo.

Following the Vioxx withdrawal, an FDA Advisory Committee decided that the cardiovascular risk was potentially a class effect and requested black box warnings for all members of the class. While it is unlikely to ever be known with certainty whether the cardiovascular effect associated with Vioxx was drug-specific or class-related, its

withdrawal, together with mixed safety data with other COX-2 inhibitors, suggests that this class will be permanently tainted. Although the FDA warning will, in fact, apply to all NSAIDs (including older non-selective products as well as the COX-2s), given that the combination of a traditional NSAID and a proton pump inhibitor (both of which are now available as generics) offers a similar GI profile to the COX-2s, doctors have increasingly reserved use of COX-2s for only those patients at greatest risk of gastrointestinal side effects. This is witnessed by the gradual decline of the largest selling COX-2 inhibitor, Celebrex, which generated $2.5bn of sales in 2011, versus $3.3bn in 2004.

Severe pain (e.g., post-operative, cancer pain)

In circumstances where NSAIDs are insufficient to alleviate pain, clinicians may turn to opioid drugs. 'Opioid' is a generic term for agents that stimulate so-called opioid receptors in the brain, triggering an analgesic effect. Opioids include both natural compounds, such as morphine and codeine, and synthetic derivatives such as meperidine, fentanyl, and methadone. The pharmacological potency of each drug is related to its affinity for opiate receptors. However, morphine continues to serve as the standard for treatment and the benchmark against which other drugs are compared.

By acting directly on the CNS as well as peripherally via inhibition of 5-HT and substance P (neurotransmitters) release, morphine is effective in most settings of acute and chronic pain, with the exception of neuropathic pain (pain due to the nervous system). However, it is associated with significant side effects, including respiratory depression and severe constipation (these effects may be alleviated by the administration of opioid antagonists, such as naloxone and naltrexone, which competitively bind to the same receptors as morphine). Additional key concerns associated with opioids are their tolerance and dependence effects. Tolerance requires increased doses of the drug over time to produce an equivalent pharmacological effect. Dependence, on the other hand, induces physical withdrawal symptoms and/or psychological cravings for the drug after its use is discontinued. Due to these complications, morphine and its peers are not recommended for long-term use, except in severe cases, such as for the treatment of cancer pain.

Neuropathic pain

Neuropathic pain, one of the large indications in this market, is a condition of chronic pain in the absence of any specific sensory nerve stimulation, and occurs as a dysfunction of the nervous system. This is related to conditions such as diabetes, alcoholism, previous amputation or shingles, but there may frequently not be any known cause. Although postulated to be related to spontaneous activity of damaged sensory nerves, the exact mechanisms behind neuropathic pain are poorly understood. It occurs in an estimated 5% of the population and is difficult to treat, with most patients on more than one drug.

Treatment of neuropathic pain has traditionally relied on the off-label use of anticonvulsants (e.g., carbamazepine) and antidepressants (e.g., tricyclic antidepressants such as amytriptyline), including Pfizer's Neurontin (gabapentin). Neurontin, which is now off-patent, may have earned as much as 50% of its historic sales from off-label use in pain management, gained official FDA approval in 2002 for use in post-herpetic neuralgia (PHN) and diabetic peripheral neuropathy (DPN). Since then, Pfizer received FDA approval for Neurontin's successor, Lyrica, for both DPN and PHN, while Eli Lilly's antidepressant Cymbalta has received approval for DPN.

Clinical end-points

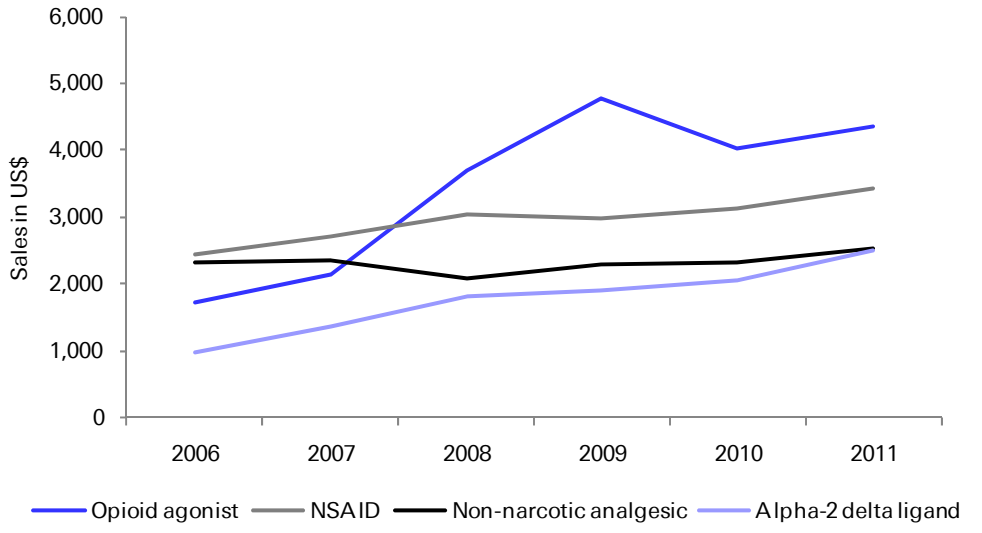
Clinical trial design varies according to the class of drugs, but usually involves the measurement of some version of a pain score from 0 (no pain) to 10 (worst pain). NSAIDs, including the COX-2s, must demonstrate pain relief equivalent to or better than that provided by gold-standard treatments such as naproxen or ibuprofen. However, in light of the Vioxx withdrawal discussed above, the safety profile of any new drug will be scrutinised very closely. The opioid-type and neuropathic pain drugs are evaluated for pain relief, primarily in comparison to morphine and placebo, respectively.

Pipeline products

Given the effectiveness of current drugs on the market (NSAIDs for mild to moderate pain, opioids for severe pain), there has not been much focus on pain as a treatment class in recent years, other than new formulations (e.g., patches). One novel approach to the treatment of pain, interestingly, has been monoclonal therapies targeting nerve growth factor. Nerve growth factor has been shown to play a role in inflammatory and neuropathic pain; hence, the use of monoclonal antibodies against this may potentially alleviate bone pain. Several companies have been developing nerve growth factor inhibitors – monoclonal antibodies found to have efficacy in treating lower back pain and osteoarthritic pain. Late-stage trials for Pfizer's tanezumab in osteoarthritis were suspended in June 2010, following worsening of osteoarthritis in some patients. Trials for other pipeline drugs of the class were suspended in December 2010 following concerns that they may be associated with rapidly progressing osteoarthritis. In March 2012, a FDA panel voted to continue research with certain restrictions & precautions, as benefits may outweigh potential risks.

Sales

Figure 215: Sales of leading analgesic classes($ m)



Source: Deutsche Bank, EvaluatePharma

Rheumatoid arthritis

- Rheumatoid arthritis (RA) affects an estimated c.1% of the population.
- Worldwide sales of drugs treating RA totalled over $26bn, a CAGR of c. 20% over 2006-11.
- Key products include TNF-α inhibitors Humira, Enbrel and Remicade.

Rheumatology refers to arthritis and over 100 other diseases affecting the joints, muscles and bones. One of the most common diseases in this group is rheumatoid arthritis (RA), a chronic syndrome characterised by inflammation of the peripheral joints, resulting in progressive destruction of the joint. Approximately 1-2% of the population is affected by RA, and one in three patients risks becoming severely disabled within 20 years of diagnosis. The onset of RA most often occurs between the ages of 25 and 50, and appears thrice as often in women than in men.

Physiology

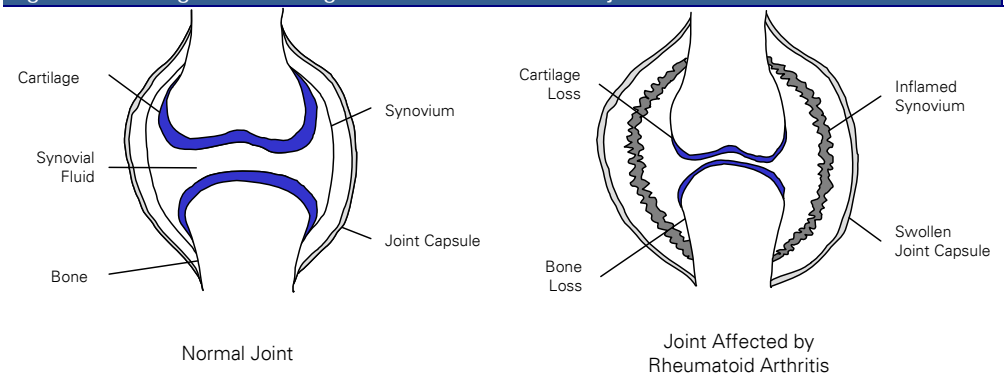
Joints comprise several essential tissues: the joint capsule, which surrounds and supports the joint; the synovium, which lines the joint capsule and produces synovial fluid; synovial fluid, which lubricates and nourishes the joint cavity; and cartilage, which covers and cushions the ends of the bones.

In RA, the body inappropriately directs a hostile immune response against cells in the joint cavity. White blood cells, called leukocytes, are recruited to the synovium and cause inflammation. The typical symptoms of arthritis, including warmth, redness, swelling and pain, occur as a result of this inflammatory reaction. The inflammatory process also causes synovial cells to grow and divide abnormally, making the normally thin synovium unusually thick and puffy. Eventually, as the abnormal synovial cells proliferate, they begin to destroy the protective cartilage and invade the surrounding bone. Concurrently, the surrounding muscles and ligaments that support the joint system also become weak. In as little as one or two years after the onset of RA, bones begin to suffer permanent damage, thus warranting early diagnosis and treatment of the disease.

Pharmacological treatment

The initial focus of RA therapy is to treat the symptoms of the disease and maintain the patient's quality of life. In addition, the long-term goal of treatment is to halt disease progression and permanent deterioration of joint tissues. While in early-stage patients, physicians have traditionally focused on pain and inflammation relief, the treatment paradigm has begun to shift, with a new emphasis on starting aggressive disease-modifying drugs earlier in the course of the disease. The key groups of RA drugs are described below.

Figure 216: Diagram showing normal vs. RA-affected joint



Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases, Deutsche Bank

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are generally used as first-line therapy for patients with mild RA. Relatively safe and inexpensive, they offer analgesic and anti-inflammatory properties that help to reduce the swelling and pain caused by RA.

Corticosteroids

Steroids, which can be administered orally or via injection directly into the affected joint, offer the most potent short-term anti-inflammatory activity but also produce significant side effects, including hypertension, osteoporosis and increased susceptibility to infection. In addition, taking steroids in the long term is associated with various side effects, which limits their role in treatment given RA's chronic nature.

Disease-modifying anti-rheumatic drugs (DMARDs)

DMARDs represent another major category of RA drugs. Unlike NSAIDs and steroids, which principally focus on short-term reduction of pain and inflammation, DMARDs attempt to halt disease progression and reduce long-term bone and joint damage. Methotrexate is the most commonly prescribed DMARD. It is an immunosuppressant, providing a more rapid onset of action and a slightly better side effect profile than other traditional DMARDs. In the event that methotrexate is not tolerated or is an ineffective monotherapy, patients may also use other DMARDs, such as sulfasalazine, chloroquine and penicillamine.

Gold compounds

Gold-containing compounds, such as auranofin (oral), aurothioglucose (injected) and aurothiomalate (injected), comprise a sub-category of DMARDs. Although not fully understood, these drugs appear to minimise the autoimmune response by interfering with lymphocyte proliferation. Additionally, auranofin appears to inhibit the induction of inflammatory cytokines, interleukin 1 (IL-1) and tumour necrosis factor α (TNF-α), both of which play an important role in normal inflammatory and immune responses. Historically used as second-line agents, gold compounds have become less popular over time due to their modest efficacy, unfavourable side effect profile and the availability of better alternatives.

TNF-α inhibitors

TNF-α is a cytokine which is found in higher concentrations in the synovial fluid of RA patients and is implicated in RA-induced inflammation. There are five TNF-α inhibitors approved for use in RA at the moment – Remicade, Humira, Cimzia, Simponi and Enbrel. The first four drugs are all monoclonal antibodies which target TNF-α. Remicade is a murine chimeric antibody, Humira and Simponi are fully humanized antibodies and

Cimzia is a PEGylated Fab fragment of a humanized monoclonal antibody. Enbrel comprises a synthetic version of the TNF receptor bound to an immunoglobulin.

Figure 217: Comparison of TNF-α inhibitors

	Enbrel (Amgen/Wyeth)	Remicade (J&J/SGP)	Humira (Abbott)	Cimzia (UCB)	Simponi (J&J)
Dose	25 mg	3-10 mg/kg	40 mg	400 mg	50 mg
ACR20 at six months (control)	65% (58%)	50% (20%)	63% (30%)	53% (13%)	60% (28%)
ACR50 (control)	40% (32%)	27% (5%)	39% (10%)	38% (8%)	37% (14%)
ACR70 (control)	21% (14%)	8% (0%)	21% (3%)	21% (4%)	20% (5%)
Dosing	twice/week	once/8 weeks	once/2 weeks	once/2-4 weeks	once/4 weeks
Administration	Subcutaneous	Intravenous	Subcutaneous	Subcutaneous	Subcutaneous
Approved as monotherapy?	Yes	No	Yes	Yes	No
Side effects	Injection site reaction	Infusion reaction, uRTI, rash, sinusitis, headache, cough	Injection site reaction, rash, back pain, uRTI, sinusitis	Injection site reaction, uRTI	Injection site reaction, uRTI, raised liver enzymes
Black box warning	Risk of infection, including tuberculosis and invasive fungal infections, and malignancy	Risk of infection, including tuberculosis and invasive fungal infections, and malignancy	Risk of infection, including tuberculosis and invasive fungal infections, and malignancy	Risk of infection, including tuberculosis and invasive fungal infections, and malignancy	Risk of infection, including tuberculosis and invasive fungal infections, and malignancy

Source: Deutsche Bank, Company data

The launch of TNF- α inhibitors has been a welcome advance in the treatment of RA. For patients who respond, TNF- α inhibitors have proven to be effective in improving symptoms and slowing disease progression. As such, they now comprise the largest class of drugs by sales in the treatment of RA. Although methotrexate is moderately effective, it is disliked by patients due to its significant and often intolerable side effects, which include nausea, vomiting, liver toxicity, chest pain, fatigue, etc. In comparison, TNF- α inhibitors' chief side effect is injection site reaction, although as a class, they have a boxed warning informing patients of the associated risk of serious infections and malignancies.

Figure 218: Sales of TNF-α inhibitors

Name	Generic	Company	2011 sales ($)
Humira	Adalimumab	Abbott Laboratories	$4.8bn
Enbrel	Etanercept	Amgen/Pfizer	$4.8bn
Remicade	Infliximab	Johnson & Johnson	$4.4bn
Simponi	Golimumab	Johnson & Johnson	$0.6bn
Cimzia	certolizumab pegol	UCB	$0.3bn

Source: Company data, Deutsche Bank, EvaluatePharma

CTLA-4 inhibitor

CTLA-4 plays a vital role in the modulation of the body's cell-mediated immune response and is a target for new therapies. Blocking the stimulation of CTLA-4 has been shown to blunt the body's immune response by inhibiting the activation of T-cells. Bristol-Myers Squibb's abatacept (Orencia) is a synthetic CTLA-4 molecule which blocks the B7 activation process of T-cells and has been approved as a monotherapy in RA, or in conjunction with DMARDs other than TNF- α inhibitors.

Anti-CD20

Roche's Mabthera is a chimeric antibody against CD20+ B-cells and was first approved for the treatment of non-Hodgkin's lymphoma. It was later approved for use in RA patients who respond inadequately to TNF- α inhibitors, in combination with methotrexate. GSK/Genmab's Arzerra is a human anti-CD20 monoclonal antibody, in

Phase III clinical trials for the same indication, while Immunomedics' Veltuzumab is in Phase II studies.

Anti-IL-6

Roche's Actemra (tocilizumab) is a humanized monoclonal antibody against interleukin-6, an important cytokine involved in activating cell- and antibody-based immune responses in chronic inflammation. Studies have demonstrated a correlation between raised interleukin-6 levels and raised inflammatory markers in RA. Actemra has been approved by the EMA as a first-line drug and by the FDA for use as a second-line drug in RA, following a failure to respond to a TNF- α inhibitor.

Arava

Arava is a synthetic, orally active drug that primarily exerts immunosuppressive activity via the interruption of pyrimidine synthesis, a key step required for T-cell proliferation. Similar in mechanism and side effects to methotrexate, it used to be a second-line agent in patients who failed to respond to methotrexate therapy but was limited by toxicity.

Kineret

Launched in 2001, Kineret (Anakinra) is a recombinant form of the naturally occurring IL-1 receptor antagonist (IL-1Ra). IL-1 is implicated in the inflammatory process and also appears to facilitate cartilage degradation. By binding to and inactivating IL-1, Kineret helps to reduce both inflammation and disease progression. However, Kineret's efficacy has proven modest, and is now often reserved as a salvage therapy in TNF inhibitor failures.

Clinical end-points

Clinical efficacy is generally evaluated using the American College of Rheumatology (ACR) response criteria, which measures improvements of 20% (ACR20), 50% (ACR50) and 70% (ACR70) from the baseline. ACR20, for example, requires a 20% decrease in the number of tender and swollen joints, as well as 20% improvements in three of the following five parameters: 1) patient's global assessment, 2) physician's global assessment, 3) patient's assessment of pain, 4) degree of disability and 5) level of acute-phase reactant (e.g. ESR). Increasingly, radiological evidence of a beneficial impact on joint destruction has been included in outcome measures of clinical trials.

Additional key considerations in clinical trial design include whether the drug is administered as a monotherapy or in combination with methotrexate, as this will define the label it later receives. In addition, trials for the new drugs typically include safety end-points.

Pipeline products

Given the favourable convenience, cost and efficacy profile of methotrexate, most new RA drugs in development typically target methotrexate failures. More recently, TNF- α inhibitors have established themselves as the new benchmark in this segment of patients. However, a high proportion of patients are usually unresponsive to their first TNF-α inhibitor, requiring a switch to a trial of another TNF-α inhibitor. This facilitates the entry of new entrants as there continues to be a demand for viable alternatives in non-responsive patients. A majority of the drugs being developed are biologics, targeting various agents involved in inflammation in auto-immune disease.

A target currently under evaluation is the Janus Kinase (JAK) enzyme. Found in immune cells, it is part of the cellular pathway involved in the production of inflammatory cytokines and proinflammatory factors. Pfizer has filed for approval of tofacitinib, an oral immunosuppressive JAK-3 inhibitor which showed positive results in RA patients when administered with methotrexate. Several tyrosine kinase inhibitors are under clinical trials: AstraZeneca's Fostamatinib is a SYK inhibitor in phase III trials for patients who fail either methotrexate or TNF- α inhibitors. Eli Lilly is studying LY3009104, a JAK-1/JAK-2 inhibitor in Phase II studies.

The RA pipeline has several interleukin antagonist MAbs being developed for subcutaneous administration. Sanofi's Sarilumab, a anti-IL6 MAb, is in phase III trials for methotrexate non-responders. Roche, UCB, GlaxoSmithKline, Johnson & Johnson and Bristol Myers-Squibb are also investigating drugs in this class. In addition, Roche is developing a subcutaneous formulation for Actemra.

In addition to these, various novel approaches to treat inflammation are under investigation. Lilly's tabalumab acts by neutralizing B-cell activating factor (BAFF), which has proved a valid target for other autoimmune diseases such as systemic lupus erythematosus. Novartis' AIN457 and Eli Lilly's Ixekizumab are IL-17 antagonists that act by suppressing inflammation associated with RA. Novo Nordisk has four biologic drugs in early stage development: NN8226 (anti-IL20), NN8828 (anti-IL21), NN8765 (anti-NKG2A) and NN8209 (anti-C5aR).

Figure 219: Selected late-stage pipeline products for rheumatoid arthritis

Name	Generic	Company	Stage	Class
Tofacitinib	Tofacitinib	Pfizer/ Takeda	Filed	JAK-3 inhibitor
Fostamatinib	Fostamatinib	AstraZeneca	Phase III	Syk inhibitor
Arzerra	ofatumumab	GlaxoSmithKline	Phase III	Anti-CD20 MAb
Sarilumab	Sarilumab	Sanofi	Phase III	Anti-IL-6 MAb
AIN457	secukinumab	Novartis	Phase III	Anti-IL-17 MAb
Tabalumab	Tabalumab	Eli Lilly	Phase III	Anti-BAFF MAb
LY3009104	LY3009104	Eli Lilly	Phase II	JAK-1/ JAK-2 inhibitor
Ixekizumab	Ixekizumab	Eli Lilly	Phase II	Anti-IL-17 MAb
Veltuzumab	Veltuzumab	Takeda	Phase II	Anti-CD20 MAb
BMS-945429	BMS-945429/ALD518	Bristol-Myers Squibb	Phase II	Anti-IL-6 MAb

Source: Company data, Deutsche Bank

Transplantation and immunosuppression

- Worldwide sales of transplant and immunosuppressive drugs totalled $6.8bn in 2011.
- Growth is primarily constrained by the availability of organs for transplant.
- Leading players include Novartis and Roche.

More than 20,000 solid organ transplants and 40,000 bone marrow transplants are performed annually worldwide. Tens of thousands more patients remain on transplant waiting lists. With patients in need far exceed the number of viable donor organs, the success of each transplant procedure is critical. This requires a good genetic matching process and effective immunosuppressive drugs to minimise the risk of rejection.

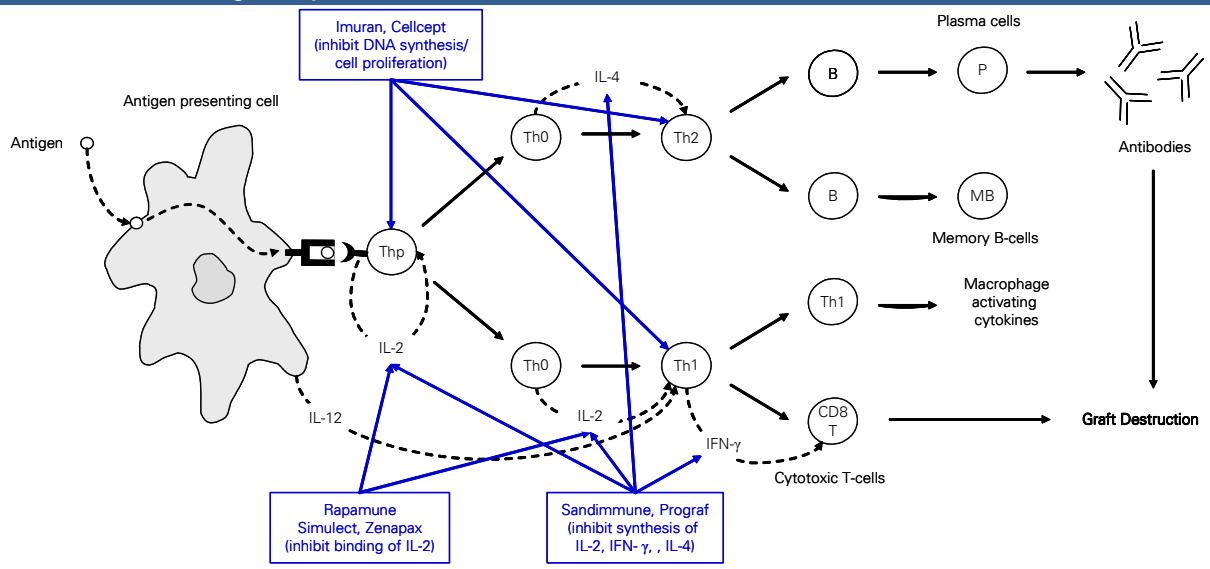
The likelihood of rejection is automatically reduced when patients receive grafts of an identical genetic nature via an autograft (use of the patient's own tissue) or an isograft (a transfer between identical twins). However, most transplants utilise allogeneic (genetically dissimilar) tissues. Because the body is conditioned to attack cells it recognises as foreign, its innate response is to reject the unfamiliar tissue. To address this, transplant patients are treated with strong doses of immunosuppressive drugs.

Physiology

When a pathogen such as a bacterium or virus enters the body, its cell surface normally exhibits antigens which the immune system recognises as foreign. Upon recognition, these antigens are taken up by certain cells, called antigen-presenting cells (APCs), which process the antigen and display it on their cell surface to uncommitted T-helper cells (Th cells). When naïve T-helper cells are presented to the antigen, they replicate and become activated T-cells (T0). T0 cells subsequently proliferate into Th1 or Th2 cells, depending on the particular cytokines present. In the Th1, or 'cell-mediated' pathway, T0 cells give rise to an army of cytotoxic CD8 T-cells capable of finding and killing infected cells. The Th2 pathway, often called the humoral response, gives rise to antibody-producing B-cells. Certain B-cells also become memory cells, which as the name suggests, remember the foreign antigen, thus enabling an immediate and potent response upon its reappearance.

Both of these pathways may lead to the rejection of transplanted allografts. When tissue from a genetically different donor is transplanted, antigens expressed on the cells of the donor's tissue trigger an immune reaction. Acute rejection is principally associated with the cell-mediated response. Late graft deterioration is thought to be caused by gradual antibody-mediated damage. In addition, some patients may experience hyperacute rejection. This reaction occurs when a patient has been previously exposed (for example, via pregnancy, blood transfusion or transplant) to cells expressing antigens identical to those on the graft. Because memory cells recall the foreign antigens, they are able to immediately proliferate and launch an attack on the newly transplanted tissue.

Figure 220: Mechanism of graft rejection



Source: Rang, Dale & Ritter, Deutsche Bank

Pharmacological treatment

To reduce the likelihood of rejection, donor tissues are tested prior to transplant to determine which antigens they express. By comparing their genetic makeup, donors and recipients may be matched so as to minimise antigenic differences. Because of residual responses (which may not have been resolved via antigen-typing), immunosuppressive drugs are also essential to the transplantation process. Given in high doses at the time of transplant, these drugs generally suppress all immune responses, making infection the leading cause of death in transplant recipients. In addition, although drug doses may be lowered over time, immunosuppressive therapy can rarely ever be stopped completely.

Historically, immunosuppression has comprised of a triple-drug cocktail of Sandimmune/ Neoral, azathioprine and a corticosteroid. Although newer agents have emerged which may be used as substitutes for Sandimmune and azathioprine, the three-pronged approach continues to persist. This triple cocktail is also the same across different types of transplant procedures, with the exception of bone marrow transplants, where methotrexate is used in place of azathioprine. Although all drugs aim to suppress the immune system in some capacity, they each act by different pathways as described below.

DNA synthesis inhibitors

Azathioprine and CellCept (mycophenolate) both suppress the immune response by interfering with the synthesis of DNA, a critical step required for cell division and proliferation. Azathioprine was first used in transplantation in the 1960s. Unfortunately, azathioprine also acts as an anti-metabolite, thus indiscriminately depleting bone marrow as well. CellCept was introduced in 1995 as a more selective alternative to azathioprine. While utilising the same underlying mechanism, CellCept blocks an enzyme called IMPDH, which is only used for DNA synthesis in lymphocytes (T-cells and B-cells). Other cells which are able to employ an alternative 'salvage' pathway are spared.

Figure 221: Standard post-transplant drug regimens

Solid organ transplant	Bone marrow transplant
Sandimmune or Prograf	Sandimmune or Prograf
+	+
azathioprine or CellCept	methotrexate
+	+
prednisone or methylprednisolone	methylprednisolone

Source: Deutsche Bank

Calcineurin inhibitors

These drugs inhibit immune cell replication by interrupting the synthesis of certain cytokines responsible for stimulating cell proliferation. Sandimmune/ Neoral (cyclosporin) bind to and inactivate calcineurin, an intracellular intermediary required in the cytokine synthesis process. However, because production is down-regulated but not entirely eliminated, affected cells preserve some ability to react against infectious agents. Prograf (tacrolimus) acts by a similar mechanism but has demonstrated a more favourable efficacy.

Corticosteroids

Corticosteroids play a role in the treatment of many diseases, but it is their immunosuppressive capability that makes them useful in transplantation. These drugs – typically prednisone or methylprednisolone – play a role in inhibiting antigen presentation, proliferation of lymphocytes and cytokine production. Circulating lymphocytes are reduced as corticosteroids induce their migration into lymphoid tissues (such as the spleen and lymph nodes).

Cytokine inhibitors

Rather than affecting the initial synthesis of cytokines, the monoclonal antibody Simulect (basiliximab) interferes with the binding of the cytokine IL-2, thereby inhibiting the proliferation of activated T-cells. J&J's Stelara (ustekinumab) binds IL-12 and IL-23 which play a role in immune responses through activation of natural killer cells and through activation and differentiation of CD4+ T-cells, respectively. Rapamune (sirolimus) and Certican (everolimus) inhibit mTOR, a protein that regulates cell proliferation.

Anti-lymphocyte agents

Orthoclone (OKT3) is a monoclonal antibody that binds to the CD3 receptor complex on T-cells, preventing them from recognising the antigens while causing cell death. Also in this category are the polyclonal antibodies, Thymoglobulin and Atgam (antithymocyte globulin), which are most often used as adjuncts, enabling the administration of other immunosuppressive drugs at lower, less toxic doses.

Figure 222: Leading transplant drugs

Name	Generic	Company	2011 sales ($)
Prograf	tacrolimus	Astellas Pharma	$1.9bn
CellCept	mycophenolate mofetil	Roche	$1.1bn
Neoral	cyclosporine	Novartis	$0.9bn
Stelara	ustekinumab	Johnson & Johnson	$0.7bn
Myfortic	mycophenolic acid	Novartis	$0.5bn
Rapamune	sirolimus	Pfizer	$0.4bn
Thymoglobulin	anti-thymocyte globulin (rabbit)	Sanofi	$0.3bn
Advagraf	tacrolimus	Astellas Pharma	$0.2bn
Certican/Zortress	everolimus	Novartis	$0.2bn
Simulect	basiliximab	Novartis	$0.1bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Clinical end-points

Key clinical end-points in transplantation trials are patient survival, graft survival and incidence of acute rejections. These measures are generally followed for a period of six to twelve months. Because of the severe consequences of ineffective drugs (i.e. graft rejection), preclinical and early clinical safety and efficacy data for novel immunosuppressants are subject to heightened scrutiny. Once in later-stage trials, the drugs are often used as incremental agents, given in addition to a traditional cocktail comprising azathioprine, Sandimmune/Neoral and/or corticosteroids.

Pipeline products

Most of the drugs currently in development attempt to offer more selective methods of immunosuppression by targeting different participants in the inflammation process. As the same immunosuppressive drugs also often find applications in auto-immune diseases such as rheumatoid arthiritis and systemic lupus erythematosus, innovators run parallel programs to investigate them for various indications.

Apart from the immune system attack that targets a transplanted organ after it is recognised it as foreign protein, there is also a localised response caused by damage to the tissue when it is deprived of oxygen while being transplanted. Astellas' Diannexin aims to contain this reperfusion injury by inhibiting the binding of monocytes and platelets to cell membrane on the transplanted tissue. Diannexin is in phase II/III trials for liver and kidney transplant.

Voclosporin is a next-generation calcineurin inhibitor that has demonstrated higher efficacy and an improved safety profile vis-à-vis cyclosporine. Isotechnika is conducting late stage trials for use of voclosporin in kidney transplant. Several companies are also developing inhaled cyclosporine formulations for use in lung transplant patients, thereby avoiding the side effects of systemic administration. Although inhaled forms are generated from iv cyclosposine solution, formal FDA approval has not been granted.

Figure 223: Selected late-stage pipeline products for transplant

Name	Generic	Indication	Company	Stage	Class
Diannexin	diannexin	Liver, kidney transplant	Astellas	Phase III	Annexin V analogue
voclosporin	voclosporin	kidney transplant	Isotechnika	Phase II/III	Calcineurin inhibitor
ASKP1240	ASKP1240	kidney transplant	Astellas	Phase II	Anti-CD40 MAb
ASP015K	ASP015K	solid organ transplant	Astellas	Phase II	JAK inhibitor

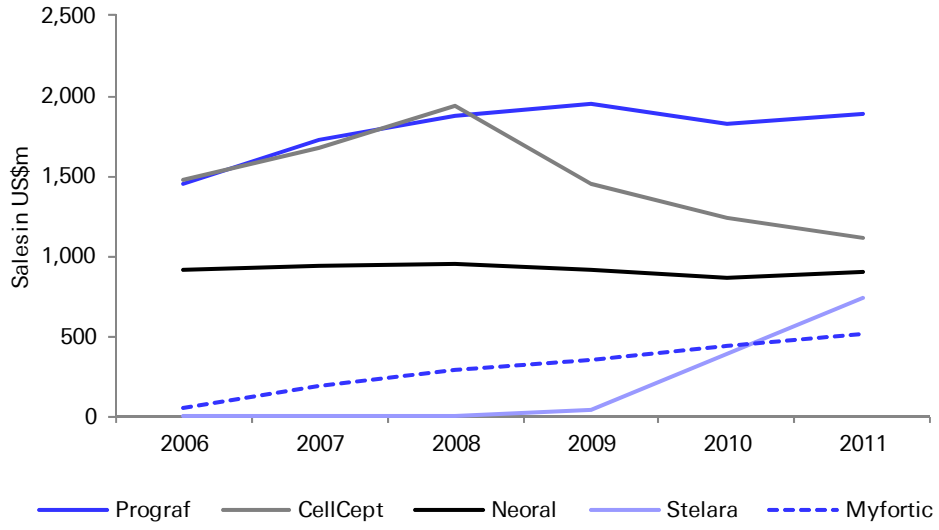
Source: Company data, Deutsche Bank

One of the challenges facing new products is physicians' reluctance to switch patients from one immunosuppressive protocol to another. This reluctance extends to switching from branded products to generic equivalents and is responsible for the ongoing high sales of branded drugs such as Neoral despite losing their patent protection years ago. Thus, the hurdle for new drugs to gain acceptance and become adopted as a standard of treatment is higher on average for the transplant category compared to other therapeutic areas.

Also limiting this sector's growth is the shortage of organs available for transplant. This is a growing area of focus for both medical researchers and drug companies. In particular, living donor transplants are becoming increasingly common for recipients requiring a kidney and even in some cases for those requiring a liver or lung transplant.

Sales

Figure 224: Sales of leading transplant drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 225: Sales of leading transplant drugs ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Prograf	Astellas Pharma	1,455	1,731	1,882	1,945	1,826	1,890
CellCept	Roche	1,471	1,679	1,942	1,455	1,241	1,121
Neoral	Novartis	918	944	956	919	871	903
Stelara	Johnson & Johnson	-	-	-	42	393	738
Myfortic	Novartis	50	193	290	353	444	518

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Antibiotics

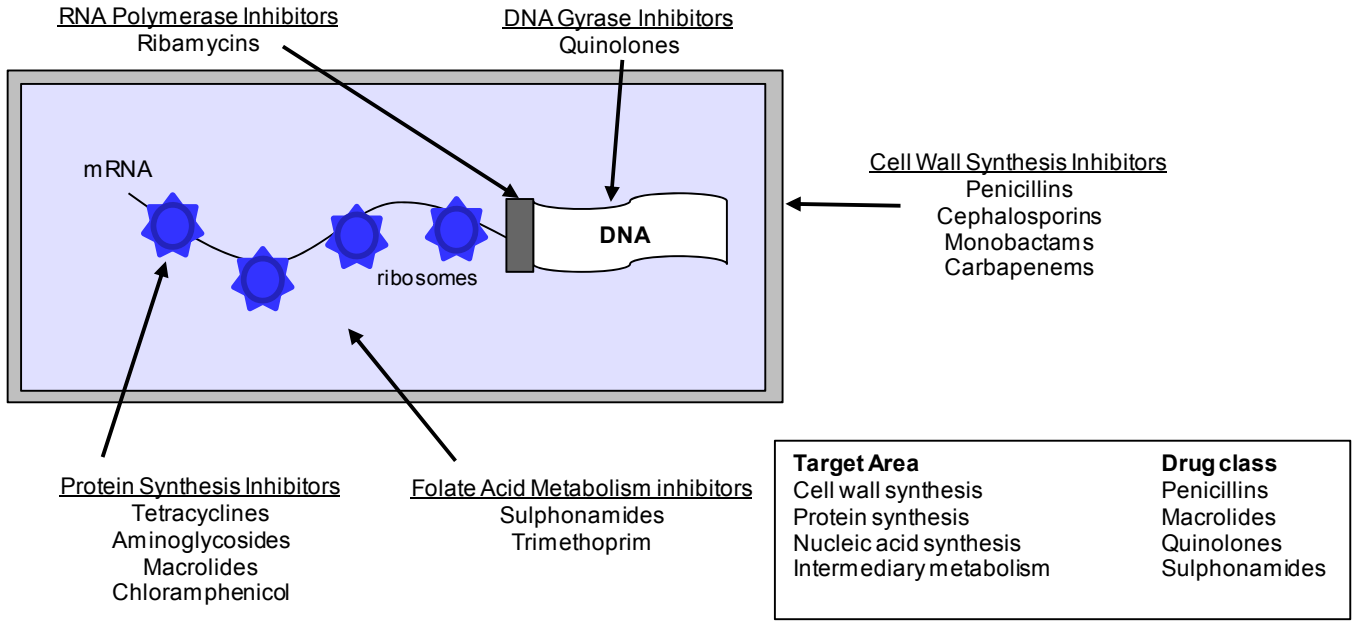
- Sales of antibiotics in 2011 totalled more than $16bn.
- Sales have seen a gradual decline due to the effect of patent expiries on key brands (such as Augmentin, Levaquin, Merrem and Primaxin).
- Resistance to traditional antibiotics is an increasing feature, but paradoxically decreases the market's attractiveness.

Antibiotics are used to kill the bacteria responsible for infections. First developed commercially in the late 1940s following Alexander Fleming's discovery of penicillin in 1928, they have played a major role in the early development of today's pharmaceutical industry. In recent years, rising resistance to existing treatments has led to renewed interest from pharmaceutical companies to develop new and effective products. However, the attractiveness of developing new therapies is limited, as these are often reserved for last-line use in multi-drug resistant bacteria, and thus commercial payback is reduced.

Physiology

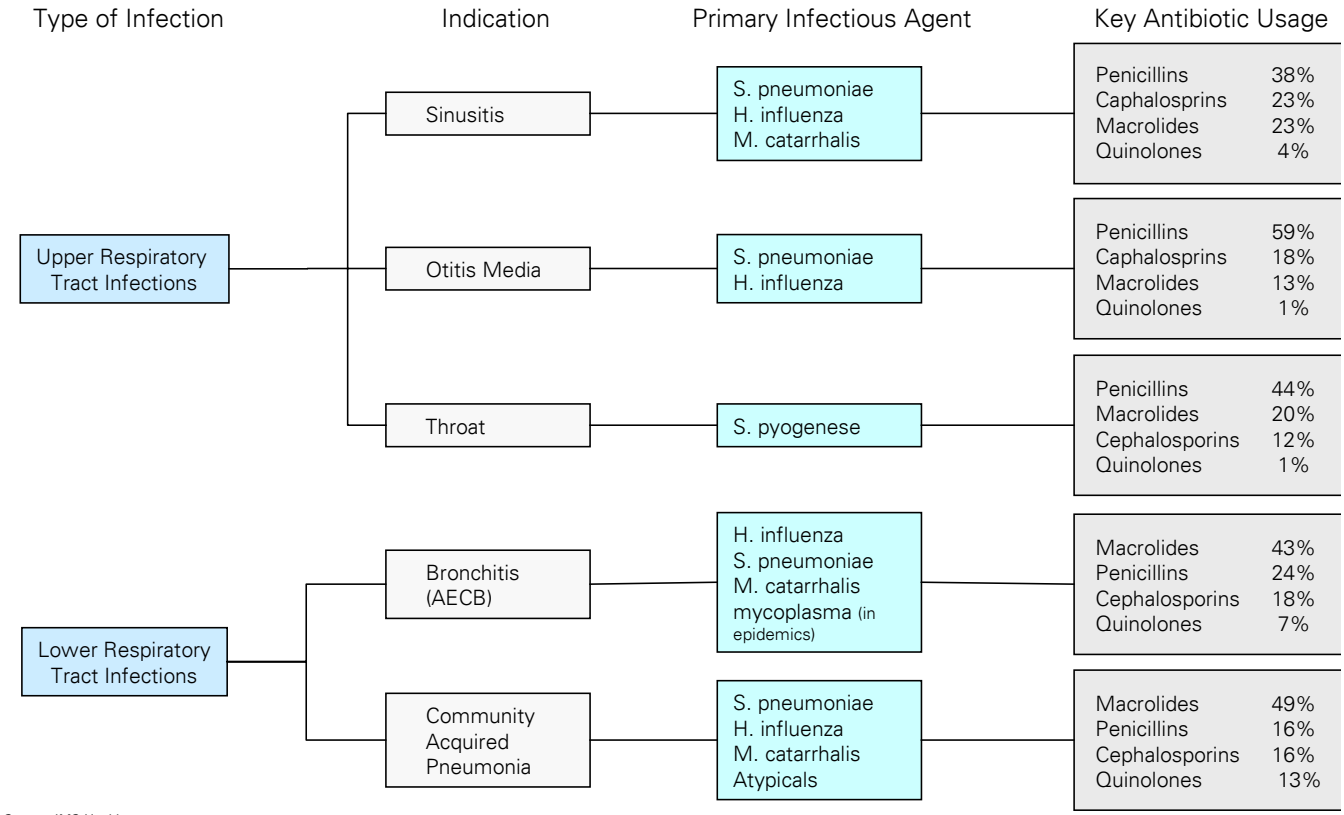
Antibiotics work by interfering with specific and essential processes within the bacterial cell. In essence, their development has centred on interfering with mechanisms and pathways that are vital to the bacteria's replication, but are either not found in humans or differ significantly. This limits, but does not completely eliminate, the drugs' toxicity to humans.

Figure 226: Antibiotics and their mode of action



Source: British Biotech, Deutsche Bank

Figure 227: Antibiotics – Respiratory tract infections and antibiotic usage



Source: IMS Health

As illustrated in Figure 227, the most frequently prescribed drugs tend to be those which inhibit cell wall synthesis (for example, β-lactams such as penicillin and cephalosporin), protein synthesis (for example, macrolides and tetracyclines), nucleic acid synthesis (quinolones) and essential intermediate pathways (for example, sulphonamides).

Bacteria are typically classed as either Gram-positive or Gram-negative. The 'Gram' definition reflects the difference in structure of the bacterial cell wall and, consequently, whether they are stained with dye in a 'Gram test'. Gram-positive bacteria tend to be associated with respiratory tract infections (RTI) and skin, while Gram-negative bacteria are associated with infections of the urinary tract (UTI) and gut. Note that almost 60% of bacterial infections are in the respiratory tract, with only 10% in the urinary tract. Respiratory tract infections (RTIs) may be further classified into those affecting the upper and lower regions.

Pharmacological treatment

Given the variety of options, the choice of treatment typically depends on several factors, not least the nature of the infection (e.g., RTI or UTI), patient history (allergic reaction to penicillin is quite common), potential drug interactions, etc. Increasingly, attention is also given to resistance, which has become a major problem. Drug usage may also be limited by the form in which the antibiotic is administered (i.e. whether it is taken orally or injected). The use of injectable antibiotics is typically limited to hospitals (a feature that generally implies more modest sales potential). The five main classes are described in Figure 228.

Figure 228: Classes of antibiotics

Class	Penicillin	Cephalosporins	Carbapenems	Macrolides	Quinolones	Oxazolidinone
Sales 2011 ($)	$2.5bn	$2.2bn	$2.1bn	$1.4bn	$3.4bn	$0.7bn
Lead product	Augmentin (amoxicillin & clavulanate)	ceftriaxone	meropenem	clarithromycin	levofloxacin	linezolid
Action point	Cell Wall (b-lactam)	Cell Wall (b-lactam)	Cell Wall (b-lactam)	Protein synthesis	DNA coiling	Protein synthesis
Side effects	Allergy	Allergy	Allergy	GI disturbance	GI, headaches	GI, headaches
Administration	Mainly oral	Mainly injected	Mainly injected	Mainly oral	Mainly oral	Oral & injected

Source: Deutsche Bank

Penicillins

Penicillin was the first modern antibiotic and is part of a larger class called beta-lactams, which includes cephalosporins and carbapenems. It acts by interfering with the synthesis of bacterial cell walls. Despite their age, penicillins remain the most widely used class of antibiotics, owing to their broad spectrum of activity and good safety profile. They remain the drugs of choice for many clinical uses, including bacterial meningitis, skin infections, pharyngitis, middle ear infections, bronchitis, gonorrhoea and syphilis, among other infections. They can be taken orally, although in some cases injections may be more efficacious. They are well tolerated and toxic side effects are rare, although allergic reactions such as rashes and fever occur in about 10% of patients. Given the group's age, many penicillins are off-patent, including the class leader of recent years, GlaxoSmithKline's Augmentin (amoxycillin + clavulanic acid), which lost its patent protection in late 2002.

Figure 229: Leading penicillins

Name	Generic	Company	2011 sales ($)
Augmentin	amoxicillin + clavulanic acid	GlaxoSmithKline	$1.0bn
Zosyn	Piperacillin + tazobactam	Pfizer	$0.6bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Cephalosporins

These are part of the β-lactam class, and interfere with the synthesis of the bacterial cell wall. Some may be taken orally but most are given by injection, making them more suitable for use in a hospital setting. They are typically used as a second-line antibiotic in conditions such as pneumonia, septicaemia, meningitis, sinusitis and urinary tract infections. Their side effect profile is similar to penicillins. The leading product is Roche's injectable Rocephin, whose patent expired in 2005. Despite their second-line usage, cephalosporins have a broader spectrum of activity compared to penicillins.

Figure 230: Leading cephalosporins

Name	Generic	Company	2011 sales ($)
Rocephin	ceftriaxone	Roche	$0.3bn
Zinnat/Ceftin	cefuroxime	GlaxoSmithKline	$0.3bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Carbapenems

These are also a form of β-lactams. Some bacteria develop resistance to β -lactams because of their ability to produce an enzyme called β -lactamase, which neutralizes the antibiotic. Carbapenems have a unique structure which makes them resistant to the action of β -lactamase. In addition, they also have a broad spectrum of action, killing both Gram-positive and -negative bacteria. Carbapenems are usually also second-line antibiotics, administered intravenously in hospitals. The leading product in this class, AstraZeneca's Merrem, lost its patent protection in June 2010.

Figure 231: Leading carbapenems

Name	Generic	Company	2011 sales ($)
Merrem	meropenem	AstraZeneca	$0.6bn
Primaxin	cilastatin & imipenem	Merck & Co	$0.5bn
Invanz	ertapenem sodium	Merck & Co	$0.4bn
Doribax	doripenem	Johnson & Johnson	$0.2bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Quinolones

The quinolones work by inhibiting a bacterial enzyme called DNA gyrase, which prevents bacterial DNA from coiling, thus preventing replication. Bayer's ciprofloxacin and Johnson & Johnson/Daiichi Sankyo's levofloxacin have been the best-selling drugs in this class. Quinolones have a broad spectrum of action, but are especially effective against Gram-negative bacteria, including organisms resistant to penicillin. Taken orally or by injection, they are most commonly used for urinary tract infections. Unwanted effects are infrequent and usually mild but include gastrointestinal disturbances and skin rashes (photosensitivity). In addition, because of their unique mechanism of action, the bacterial resistance mechanisms that have limited the efficacy of other antibiotics, do not affect quinolones. Hence they can be effective against organisms to which other drugs are ineffective. However, widespread use has led to emergence of resistance to the class. This can emerge rapidly, even during treatment. Sales growth of the class has declined due to patent losses, most recently that of levofloxacin in 2011. (ciprofloxacin lost patent protection in 2004).

Figure 232: Leading quinolones

Name	Generic	Company	2011 sales ($)
Levaquin	levofloxacin	Johnson & Johnson	$0.6bn
Avelox	moxifloxacin	Bayer	$0.6bn
Cravit	levofloxacin	Daiichi Sankyo	$0.5bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Macrolides

Macrolides such as erythromycin have been in use for over 40 years. They interfere with bacterial protein synthesis by attaching to bacterial ribosomes (the cellular constituents that read RNA as a template for protein synthesis). Their spectrum of activity is similar to that of penicillins, and they have proven useful alternatives in patients who are allergic to penicillins. They are typically administered orally, with the main unwanted side effects being gastrointestinal disturbances.

Figure 233: Leading macrolides

Name	Generic	Company	2011 sales ($)
Biaxin/Klacid	clarithromycin	Abbott Laboratories	$0.5bn
Zithromax	azithromycin	Pfizer	$0.5bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Antibiotic resistance

Poor compliance and over-prescribing, among other reasons, have meant that bacterial resistance to antibiotics is an increasing problem. After years of exposure and consequent mutation, many forms of bacteria have become resistant to an increasing number of antibiotics. Initially more prevalent in hospital settings, resistance is now an increasing threat in community-acquired infections.

There are several mechanisms of resistance. For example, bacteria have become capable of synthesising beta-lactamases that cleave the beta-lactams before they can be fully effective. Alternatively, bacterial mutation may mean that initial drug targets have now been modified. These resistance mechanisms have primarily limited the use of penicillin, cephalosporins and other beta-lactams in the treatment of certain diseases. Resistance to the quinolones is also a growing problem. Target alteration has also limited the use of erythromycin and some other macrolides.

Common antibiotic-resistant bacteria include MRSA, or methicillin-resistant staphylococcus aureus, which is a bacterium commonly responsible for skin infections that have become resistant to beta-lactam antibiotics. Equally, enterococcus, a frequently encountered hospital pathogen, now shows resistance to vancomycin (vancomycin-resistant enterococcus, or VRE), a drug which had previously been the antibiotic of last resort.

Hence, antibiotic resistance presents a major threat to the treatment of disease. Tried and trusted antibiotics may no longer work on bacteria against which they had previously proven efficacious. However, this situation also offers an opportunity to try novel new classes of antibiotics.

Pipeline products

The antibiotic pipeline has few new products; compounds in development phase represent variations of existing antibiotic classes, targeted at resistant strains of bacteria, improved delivery systems to minimise side effects, or antibiotic combination products. While there is an unequivocal medical need for such alternative treatments, it is important to note that restriction of use of modern agents to later line resistant strain treatment may nonetheless limit their commercial potential.

Forest Labs/AstraZeneca's Teflaro/Zinforo (ceftaroline) has been approved by the FDA and received a positive opinion from CHMP for the treatment of skin and soft tissue infections and community acquired pneumonia. The drug represents a next-generation cephalosporin antibiotic, with a broad spectrum of activity against Gram-positive and Gram-negative bacteria. It is also active against MRSA.

Human Genome Sciences is developing ABthrax (Raxibacumab), an antibody to treat toxins released in blood and tissues on infection with inhaled anthrax. While antibiotics are available against the anthrax bacteria, high mortality is associated with production of toxins. The drug is being developed under a contract with the US HHS Department, and primary application would be to counter use of anthrax as a biological weapon. HGS has resubmitted ABthrax to the FDA after its initial 2009 submission elicited requests for additional data and further analysis.

CAZ/ AVI is AstraZeneca/ Forest's phase III combination of ceftazidime and avibactam, a broad spectrum combination aimed at treating serious gram-negative bacterial infections in hospitalized patients. Phase II studies in patients with complicated intra-abdominal infection or urinary tract infection showed response rates similar to those with existing lines of therapy, with good tolerability.

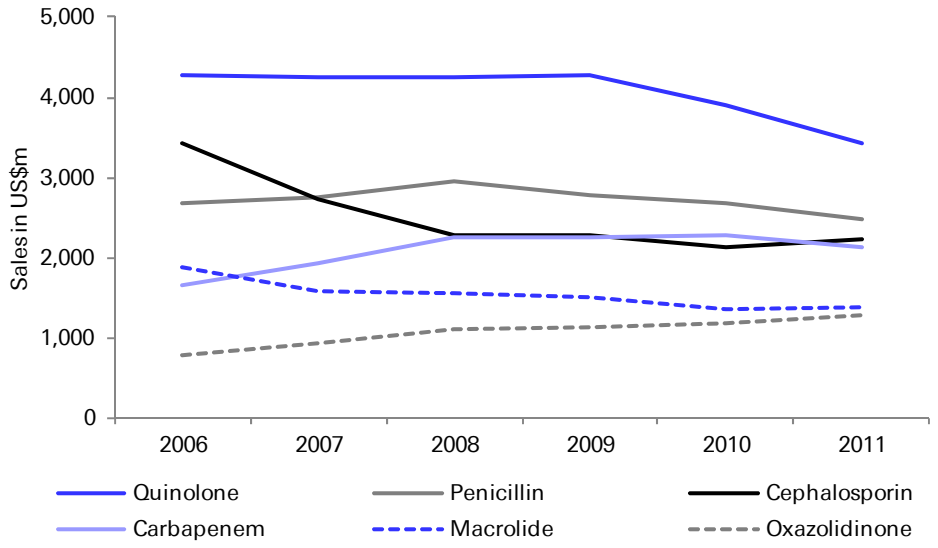
Figure 234: Selected late-stage pipeline antibiotics

Name	Generic	Company	Phase
Zinforo	ceftaroline	AstraZeneca	Filed
ABthrax	raxibacumab	Human Genome Sciences	Filed
CAZ AVI	Avibactam + ceftazidime	AstraZeneca/ Forest	Phase III

Source: Company data, Deutsche Bank

Sales

Figure 235: Sales of antibiotic classes



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 236: Sales of antibiotic classes ($ m)

Class	2006	2007	2008	2009	2010	2011
Quinolone	4,286	4,249	4,240	4,276	3,896	3,431
Penicillin	2,674	2,752	2,941	2,776	2,685	2,488
Cephalosporin	3,421	2,723	2,275	2,287	2,137	2,219
Carbapenem	1,651	1,932	2,251	2,249	2,287	2,127
Macrolide	1,872	1,583	1,558	1,505	1,344	1,369
Oxazolidinone	782	944	1,115	1,141	1,176	1,283

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Human immunodeficiency virus (HIV)

- Sales of HIV-related drugs totalled more than $16bn in 2011.
- Approximately 34m people were infected worldwide in December 2010, including 1.2m in the US, 1m in Western and Central Europe and 22.9m in sub-Saharan Africa.
- Combination therapy is key to treatment.
- Key companies are Gilead Sciences, ViiV healthcare (joint venture of GlaxoSmithKline and Pfizer), and Bristol-Myers Squibb.

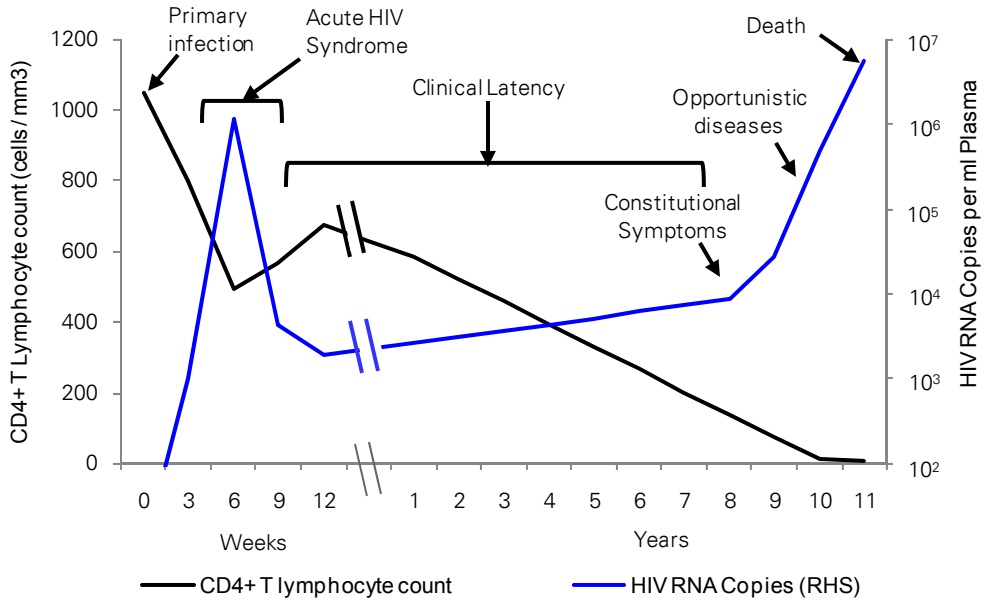
Acquired immunodeficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV). The virus causes disease by replicating in the white blood cells of the immune system and destroying them in the process. Bereft of their resistance to disease, HIV-infected individuals eventually become susceptible to opportunistic infections and fast-growing cancers, which are the usual cause of death in these individuals. Market growth for HIV drugs in recent years has been strong, driven by a number of factors, including the development of new drugs, acceptance that drug treatment has a beneficial effect on prognosis, growing use of combination therapy and the issuance of treatment guidelines promoting earlier initiation of therapy. The efficacy of current regimens has also spurred drug growth, as patients live longer on multi-drug regimens.

Physiology

Viruses are small infective agents (virions) essentially consisting of a few genes enclosed in a protein coat called a capsid. They are intracellular parasites with no metabolic machinery of their own. Simplistically, viruses initiate infection by attaching themselves to host cells and then entering them through a process called endocytosis. The nucleic acid of the virus (which in HIV is a strand of RNA) then uses the host cell's replication machinery to multiply its genetic code (nucleic acid), as well as the proteins needed for assembly of new viral capsids. Host cell death follows, releasing the newly assembled virions, which go on to infect other cells.

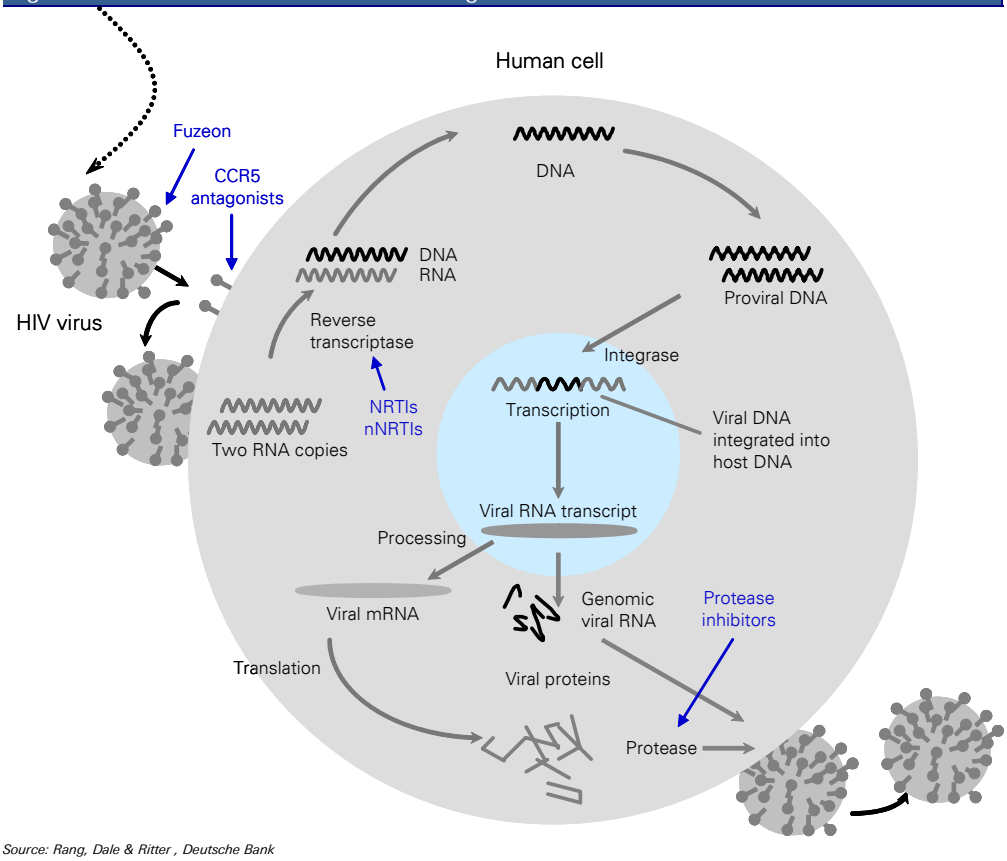
In a patient infected with HIV, the virus binds to a particular class of white blood cells called helper T-cells or CD4 cells, which play a key role in the body's natural immune defences. During the initial infection, there is a progressive loss of CD4 cells, this being the defining characteristic of HIV infection, and the viral count in the host's blood (the viral load) increases markedly. As antibodies to the infected CD4 cells are produced by the body's still-functioning immune system, the infected CD4 cells are killed and with them, the virions inside. Consequently, the viral load declines sharply in the earlystage sof infection. However, because viral replication with the HIV virus is error prone, constant mutations occur. While the body's immune system consistently produces antibodies to the new variants, it is postulated that wave after wave of mutations gradually deplete the body's ability to respond. Thus the virus eventually gains the upper hand. The viral load then starts to rise again, and when the body's immune system is no longer able to ward off other opportunistic infections, full-blown AIDS (Acquired Immune Deficiency Syndrome) develops. In the absence of drug therapy, death usually follows within two years, caused by a host of opportunistic diseases.

Figure 237: Illustration of progression from HIV to AIDS



Source: Adapted from Pantaleo et al, 1993, Deutsche Bank

Figure 238: HIV infection and sites of drug action



Source: Rang, Dale & Ritter , Deutsche Bank

Pharmacological treatment

As with antibiotics used against bacteria, the development of drugs to treat HIV has centred on inhibiting metabolic processes that are specific to the virus. Historically, treatments focused on three main mechanisms of action, leading to the emergence of three main classes of drug in the 1990s: the nucleoside reverse transcriptase inhibitors, or NRTIs; the non-nucleoside reverse transcriptase inhibitors, or nNRTIs; and the protease inhibitors, or PIs. However, a few new novel classes of drugs have emerged in the past decade – fusion inhibitors, CCR5 antagonists and integrase inhibitors. The mechanism of each is briefly described below. However, it should be stressed that while the discovery of several new drugs to treat the HIV virus has extended the lives and prospects for HIV-positive patients, up to 40% of patients may be on their third or fourth combination regimen because of therapy failure or resistance.

NRTIs (nucleotide/nucleoside reverse transcriptase inhibitors)

This class of drug (which was the first to be approved for HIV treatment in the late 1980s, in the form of GSK's Retrovir or AZT) binds to the active site of the reverse transcriptase enzyme, inhibiting the replication of a virus in the cell. Following viral entry into the CD4 cell, the reverse transcriptase enzyme is responsible for transcribing viral RNA to DNA, nucleotide by nucleotide. The NRTI binds to the enzyme and is inserted into the new DNA chain instead of a nucleotide. This prevents further transcription of the DNA chain, thereby stopping the creation of a new virus. Global sales of this class in 2011 were around $5.5bn. Side effects include gastrointestinal disturbances, with more severe side effects of lactic acidosis and hepatomegaly. NRTIs are also available as combination products and include Gilead Sciences' Truvada (tenofovir + emtricitabine) and ViiV Healthcare's Epzicom/Kivexa (lamivudine + abacavir). Several drugs of this class, plus combinations containing NRTIs, have lost patent protection over the 2010-2012 period (Epzicom, Combivir, Zeffix, Trizivir, Epivir).

nNRTIs (non-nucleoside reverse transcriptase inhibitors)

nNRTIs also bind to and inhibit the reverse transcriptase enzyme, but not at its active site. The reverse transcriptase enzyme of HIV-2 variant has a different structure and is resistant to nNRTIs. Hence, nNRTIs are mostly restricted to infections by the HIV-1 variant. Sales of nNRTIs in 2011 were around $1bn. Side effects include headaches, dizziness and rashes. Johnson & Johnson's Intelence (etravirine) bettered Bristol-Myers Squibb's Sustiva (efavirenz) in both efficacy and side effect profile in late stage trials. The drug was approved in 2008 and has rapidly become the top selling drug in this class. Leading nNRTIs include Intelence, Sustiva and Boehringer Ingelheim's Viramune (nevirapine), of which the latter two are set to lose patent protection over 2012-13. nNRTIs are usually prescribed in combination with NRTIs, such as the blockbuster combination drug, Atripla. FDA and EMA also approved Gilead's Complera in 2011. Sales for NRTI-nNRTI combination products were over $3bn in 2011.

PIs (protease inhibitors)

This class of drug, also known as HIV-1 protease inhibitors because of their specificity for HIV-1, acts on a different enzyme than the other two classes. Following infection with the HIV virus, proviral DNA is created by reverse transcriptase, which is then the template for the production of various proteins. These proteins are then cut and spliced to assemble the final mature virus. Protease inhibitors target this final process, and hence interfere with the production of new viruses. However, a change of even one amino acid makes the enzyme unrecognizable by protease inhibitors. Hence, HIV's high rate of mutation makes resistance a key challenge for protease inhibitors and, therefore, protease inhibitors are seldom used alone in therapy. Furthermore, there are many side effects, not least gastrointestinal disturbances, nausea and lipodystrophy (fatty humps

develop on patients' backs). Sales of this class in 2011 were c.$5bn. Leading PIs include Bristol-Myer Squibb's Reyataz (atazanavir), Johnson and Johnson's Prezista (darunavir) and Abbott Laboratories' Kaletra (ritonavir + lopinavir).

Fusion inhibitors

Fusion inhibitors attempt to prevent the HIV virus from infecting the CD4 cell by interfering with a protein on the surface of the viral envelope, thereby preventing the virion's attachment to the target cell. The only currently marketed product in this class is Roche/Trimeris' Fuzeon, which generated sales of c.$92m in 2011. It is administered via subcutaneous injection twice a day and its action is limited to the HIV-1 variant. Its inconvenient dosing and high cost has limited its use to a salvage role, when patients become resistant to other classes of medication.

CCR5 antagonists

CCR5 is one of the receptors on the cell surface which is required for HIV viruses to enter and infect CD4 cells. The importance of this receptor was discovered after analyzing a segment of high-risk individuals and discovering that they had a mutation in the gene coding for CCR5, which conferred a resistance to the HIV virus. However, HIV viruses which are able to bind to an alternate receptor, CXCR4, will still be able to infect the cell. Therefore, a co-receptor tropism assay testing for CCR5, CXCR4, or both, is required before initiation of therapy with a CCR5 antagonist. Currently, the only member in this class is ViiV's Selzentry/Celsentri (maraviroc), which binds to CCR5, blocking attachment of CCR5-tropic HIV-1 viruses. Side effects include diarrhoea, upper respiratory traction symptoms and fever. Sales were just under $0.2bn in 2011.

INSTIs (integrase strand transfer inhibitors)

Integrase inhibitors work by blocking the integrase enzyme, which is responsible for integrating the viral genetic material into the host DNA for transcription and replication of new viral genetic material. The only member of this class is Isentress (raltegravir), and it is indicated as usual for the treatment of HIV-1 in combination with other HIV medications. Its side effects are relatively mild and it is well-tolerated. 2011 sales of Isentress were c.$1.4bn. Two new integrase inhibitors are expected to be approved in the next year, beginning with Gilead's elvitegravir (as a monotherapy or part of a novel quadruple combination product, Quad) and followed by ViiV's dolutegravir (as a monotherapy or part of a triple combination with Epzicom/Kivexa).

Figure 239: Leading anti-HIV drugs/ combinations

Name	Generic	Class	Company	2011 sales ($)
Atripla	efavirenz; emtricitabine; tenofovir	NRTI + nNRTI	Gilead Sciences	$3.2bn
Truvada	emtricitabine; tenofovir	NRTI	Gilead Sciences	$3.0bn
Reyataz	atazanavir	PI	Bristol-Myers Squibb	$1.6bn
Isentress	raltegravir	INSTI	Merck & Co	$1.4bn
Prezista	darunavir	PI	Johnson & Johnson	$1.3bn
Kaletra	lopinavir; ritonavir	PI	Abbott Laboratories	$1.2bn
Epzicom/Kivexa	abacavir; lamivudine	NRTI	ViiV (GSK/Pfizer)	$1.0bn
Combivir	lamivudine; zidovudine	NRTI	ViiV (GSK/Pfizer)	$0.5bn
Norvir	ritonavir	PI	Abbott Laboratories	$0.4bn
Intelence	etravirine	nNRTI	Johnson & Johnson	$0.3bn
Viread	tenofovir	NRTI	Gilead Sciences	$0.3bn
Viramune	nevirapine	nNRTI	Boehringer Ingelheim	$0.3bn
Sustiva	efavirenz	nNRTI	Bristol-Myers Squibb	$0.3bn

Source: Company data, EvaluatePharma, Deutsche Bank estimates

Treatment protocol

Antiretroviral therapy has changed dramatically in recent years. Data suggesting that treatment with three-drug regimens could, in theory, completely suppress viral replication have driven the acceptance of combination therapy as the standard method of treatment for HIV-infected patients. Initially, treatment guidelines recommended the use of two NRTIs with one PI. However, concerns over metabolic side effects associated with PIs have seen some switching to the use of an nNRTI instead. Currently, the National Institute of Health Panel on Antiretroviral Guidelines for Adults and Adolescents (since March 2012) recommend the following combinations as preferred initial regimens:

- **nNRTI-based**: nNRTI + 2 NRTI, e.g. efavirenz + tenofovir + emtricitabine (which constitute Gilead's market-leading combination drug Atripla)
- **PI-based**: PI + 2NRTI, e.g. ritonavir-boosted atazanavir/darunavir + tenofovir + emtricitabine
- **INSTI-based**: INSTI + 2NRTI, e.g. raltegravir + tenofovir + emtricitabine

Given the number of drugs taken, compliance with highly active anti-retroviral therapy (HAART) is a major issue. Consequently, drug manufacturers have sought to develop combination tablets, such as GSK's Combivir and Trizivir and Gilead's Truvada and Atripla.

Because of the degree of mutation of the HIV virus, viral resistance remains a major issue. In an effort to limit resistance with current drugs, there has been considerable debate as to the most appropriate time to start treatment. Current US guidelines recommend treatment for all HIV infected individuals. Furthermore, in July 2012, the FDA approved Gilead's Truvada (emricitabine + tenofovir) to reduce the risk of acquiring HIV infection, the first drug to be approved for pre-exposure prophylaxis.

Figure 240: US HIV treatment protocol

Clinical category	CD4 and HIV count	Strength of Recommendation
Symptomatic (AIDS evident)	Any value	Strong
Pregnant	Any value	Strong
HIV associated nephropathy	Any value	Strong
HIV/hepatitis B virus (HBV) coinfection	Any value	Strong
Asymptomatic	CD4<350 cells/mm3	Strong
Asymptomatic	CD4 between 350-500 cells/mm3	Strong
Asymptomatic	CD4>500 cells/mm3	Moderate

Source: National Institutes of Health Panel on Antiretroviral Guidelines for Adults and Adolescents

Clinical end-points

The two primary clinical measures are CD4 counts and viral load counts. CD4 counts are a measure of immune function for HIV-infected patients as well as being an accurate indicator of subsequent disease progression and survival. Viral load is also important because it measures a patient's response to anti-retroviral therapy, and reduction in viral load has been clinically correlated with improved outcomes. In addition, the count should be taken after several different periods of treatment in order to establish whether the impact on HIV is sustained or transitory.

Pipeline products

Though anti-retroviral therapy has been quite successful in reducing AIDS-associated morbidity and mortality, drug resistance remains an obstacle, compounded by poor compliance. Drugs under development, therefore, primarily seek to address these issues. The first marketed integrase inhibitor, Isentress (raltegravir), met with considerable success, given its strong efficacy and benign safety profile. This class of drugs leads the HIV pipeline, with new investigational drugs from Gilead, ViiV Healthcare, Merck and Boehringer Ingelheim.

Gilead has already filed with FDA and EMA for approval for its once-daily integrase inhibitor, elvitegravir. Late stage clinical studies reported that the drug was comparable to Isentress in efficacy and side effect profile. Gilead has also filed approval for a combination once-daily pill, Quad, which is an INSTI based-treatment, consisting of elvitegravir, Truvada (emtricitabine + tenofovir) and a novel booster, cobicistat. The last is not an anti retroviral drug, but instead inhibits the metabolism of elvitegravir – this boosts the level of drug in the body and thus allows once-daily dosing. An FDA AdCom in May 2012 voted 13:1 in favor of approval for Quad and an FDA approval is expected around the time of publication of this report (the PDUFA date is 27 August 2012).

ViiV Healthcare's dolutegravir is an integrase inhibitor in phase III trials; phase II studies reported efficacy better than Sustiva (efavirenz) and comparable to Isentress. ViiV is also studying a dolutegravir-based regimen (INSTI-based treatment) by combining the drug with Epzicom/Kixeva (abacavir + lamivudine). The phase III SINGLE study demonstrated superiority to Atripla, primarily driven by a higher rate of discontinuations in the Atripla arm for side effects. The 'cure' rates (reduction in viral load to undetectable levels) were similar for the dolutegravir combination and that reported in phase III trials of Quad. Regulatory filing of ViiV's product is likely in early 2013, so that Gilead looks set to have at least a year's headstart with its next generation product.

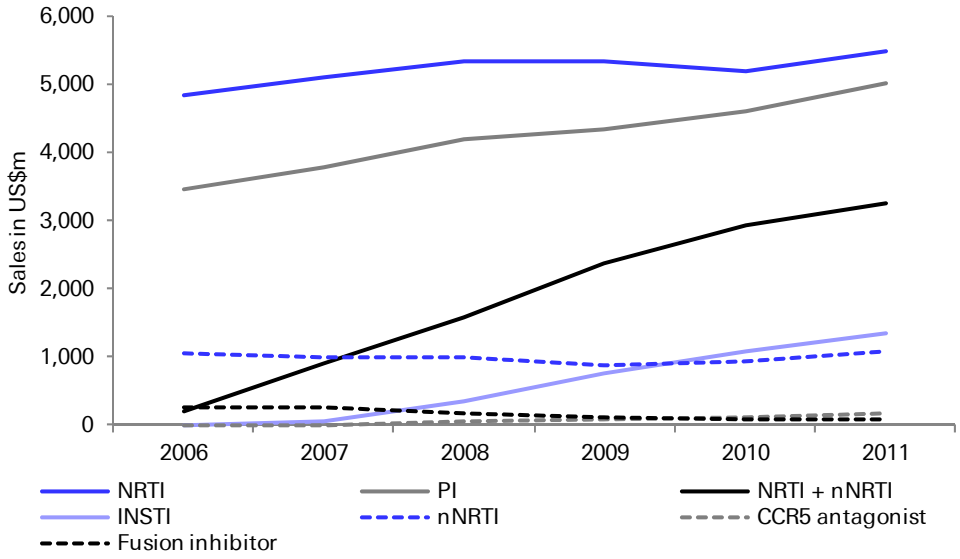
Figure 241: Selected late-stage pipeline HIV drugs

Name	Generic	Class	Company	Status
Elvitegravir	elvitegravir	INSTI	Gilead Sciences	Filed
Quad	cobicistat; elvitegravir; emtricitabine; tenofovir	NRTI + INSTI + CYP3A inhibitor	Gilead Sciences	Filed
Dolutegravir	dolutegravir	INSTI	ViiV Healthcare	Phase III
Dolutegravir-Trii/ 572-Trii	abacavir; dolutegravir; lamivudine	NRTI + INSTI	ViiV Healthcare	Phase III
UK-453061	lersivirine	nNRTI	ViiV Healthcare	Phase II

Source: Deutsche Bank, Company data

Sales

Figure 242: Sales of HIV drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 243: Sales of HIV drugs ($m)

Class	2006	2007	2008	2009	2010	2011
NRTI	4,821	5,096	5,346	5,338	5,193	5,481
PI	3,445	3,770	4,191	4,328	4,593	5,004
NRTI + nNRTI	206	903	1,572	2,382	2,927	3,263
INSTI	-	41	361	752	1,090	1,359
nNRTI	1,062	980	995	867	930	1,079
CCR5 antagonist	-	9	46	97	124	176
Fusion inhibitor	249	267	167	112	88	92

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Viral hepatitis

- Global sales of viral hepatitis-related drugs and vaccines totalled c.$8bn in 2011.
- The two major markets are Hepatitis B (HBV) and Hepatitis C (HCV).
- More than 350m people worldwide are chronically infected with HBV and 150m with HCV.
- Major players include Roche, Bristol-Myers Squibb and Merck.

Viral hepatitis is a major cause of disease and death worldwide. At least five different clinically important variants have been discovered, the two most significant of which, Hepatitis C (HCV) and Hepatitis B (HBV), account for up to 80% of chronic disease. However, the vast majority of carriers are not aware that they are infected with the virus.

Physiology

Hepatitis B and C are typically spread through blood and thus are most commonly associated with intravenous drug use or infected blood products. They can also be transmitted through sexual intercourse, and are estimated to be 100 times more contagious than HIV via that route. As the name suggests, the virus congregates and replicates in liver cells (or hepatocytes), using the host's cellular apparatus to replicate. Their infection may cause varying degrees of liver inflammation, which are categorized clinically by the duration or severity of the infection. In acute hepatitis, the viral infection may last up to six months, during which time patients experience mild symptoms, such as fatigue, malaise, anorexia, and in about 25% of cases, jaundice (yellow skin). Most patients with acute infection experience only minimal long-term liver cell damage.

About 65% of patients infected with HBV recover completely. However, approximately 10% of adults and up to 90% of infants do not clear the virus within six months and develop chronic or persistent infection. Without treatment, these patients are likely to carry the disease for the rest of their lives. While many of them may show no symptoms for long periods of time, if at all, a significant proportion will go on to develop liver cirrhosis (liver inflammation with scarring) or even cancer of the liver. At the present time, it is thought that up to 350m people worldwide have chronic HBV. The vast majority is in South-East Asia and Africa, where as much as 8-10% of the population may be infected. In the US and Western Europe there are roughly 1.25 million and 3 million chronic sufferers, respectively. In the US, roughly 10% of chronic liver disease and cirrhosis is thought to be caused by secondary effects of chronic HBV infection.

By contrast, in HCV infection, a far higher percentage of people infected fail to eradicate the virus within six months. Up to 80% of patients infected with HCV develop chronic infection, of whom a significant minority will suffer from liver cirrhosis and liver cancer. The number of patients that develop chronic HCV means that it is now the leading cause of liver transplants in the US. It is estimated that there are now more than 180m carriers worldwide, predominantly in Africa, South East Asia and Latin America, with some 12m people in the major Western economies with the disease. Importantly,

of the 3.2m infected in the US, around only 20% have been diagnosed and just 5% have elected to receive treatment.

Pharmaceutical treatment of chronic viral HBV

Vaccines are available for prophylaxis against infection, but once infected, no known drug can consistently eradicate HBV. Current therapeutic options include antiviral agents and immunomodulatory agents, such as interferons, which affect viral replication and alter the immune response against the virus. In light of the large potential market and the negative sequelae associated with chronic infection, the development of an effective treatment is seen to be potentially lucrative.

Interferons

Traditionally, treatment has been based around the use of the alpha-interferons, which were introduced by Roche and Schering-Plough in the US market in 1992. These drugs enhance the immune response against the virus, leading to a complete loss of HBV DNA and normalisation of certain liver enzymes (serum aminotransferases) in 33% of patients. A small percentage of responders relapse following the cessation of therapy (this is in marked contrast with HCV, where almost 50% relapse). However, interferon is very expensive and efficacy is limited. Side effects, such as flu-like symptoms and bone marrow suppression, also result in the discontinuance of therapy in up to 10% of patients.

Antivirals

Aside from interferon, certain nucleoside reverse transcription inhibitors (NRTIs), which are traditionally used for HIV treatment, have been found to have a therapeutic effect. The first to be used was GlaxoSmithKline's Zeffix (lamivudine). Three-year clinical data have shown that 65% of patients taking this drug experience a loss of viral antigen, though resistance (not yet seen to be clinically relevant) is steadily becoming a feature. Bristol-Myers Squibb's nucleoside analogue, Baraclude (entecavir), demonstrated superiority over lamivudine in treatment-naïve patients, with up to 90% of patients achieving a viral load of <300 copies/ml, and is also approved for use in lamivudine-resistant patients.

Beyond treatment of the disease, there is also a substantial market for Hepatitis B vaccines, which in 2011 had sales of c.$1.2bn. GlaxoSmithKline's vaccine franchise commands nearly half this market, and includes combinations of hepatitis A & B vaccines as well as Pediarix, which provides active immunity against hepatitis B, diphtheria, pertussis, tetanus and poliomyelitis. Vaccination results in protection for more than 90% of healthy persons.

Pharmaceutical treatment of chronic viral HCV

As with HBV, the objective of treatment in HCV is to achieve an undetectable viral load and normal liver enzyme levels six months after the cessation of therapy, that is, attain a sustained response. It is also important to recognise that in HCV, there are six different viral genotypes. Crucial here is that the two most prevalent genotypes, 1a and 1b, which account for 70% of chronic HCV infections, are also the hardest to treat. This is seen from analysis of response profiles, where patients with genotype 2 or 3 achieve a 40% response with interferon alone, against a 10% response rate for genotype 1.

Until recently, the traditional standard of treatment for HCV was dual therapy with alpha interferon and an adjunct called Rebetol (ribavirin). In the US, Schering-Plough

had rights to this combination, bundling the two products together in a package called Rebetron. However, the virus often responded poorly to this conventional therapy, most likely as a result of the rapid rate at which injectable interferon is broken down by the body and, consequently, its low bioavailability. In an attempt to overcome this, both Schering-Plough and Roche developed pegylated interferon. Merck's PEG-Intron and Roche's Pegasys have a molecule of polyethylene glycol (PEG) attached to them, which reduces the rate at which interferon degrades in the body. In addition, they can be given once a week compared with traditional regimens, which require injections three times a week.

Schering-Plough received approval for PEG-Intron in January 2001, followed by approval for the drug in combination with ribavirin approximately one year later. Roche received approval for Pegasys in October 2002, followed by approval two months later for its own ribavirin (called Copegus) to be used in combination with Pegasys. Since its launch, Pegasys has gained market share to become the class leader, with sales of c.$1.6bn vs. c.$650m for PEG-Intron in 2011. In a head-to-head study comparing Pegasys with PEG-Intron (The IDEAL study), patients receiving Pegasys had a higher response rate, while patients receiving PEG-Intron had a lower relapse rate, such that overall sustained response rates were comparable in both groups. However, a meta-analysis of 12 trials involving both drugs showed that Pegasys had a slightly higher response rate than PEG-Intron.

Figure 244: Comparison of Pegasys and PEG-Intron efficacy

	Pegasys		PEG-Intron		Pegasys + Ribavirin		PEG-Intron + Ribavirin	
Genotype	Make-up	Sustained response	Make-up	Sustained response	Make-up	Sustained response	Make-up	Sustained response
Genotype 1	63	28	70	14	n.a.	46	68	42
Non-1	37	58	30	51	n.a.	76	32	82
Total	100	39	100	25	100	56	100	54

Source: European Association for the Liver; American Association for Study of Liver Diseases

The treatment paradigm evolved further in 2011 when the FDA approved two protease inhibitors for the treatment of treatment of genotype 1 chronic hepatitis C – Merck's Victrelis (boceprevir) and Vertex Pharma's Incivek (telaprevir). Protease inhibitors (or direct acting antivirals) play an important role blocking the final stage of the viral maturation process, where proteins are cut and spliced to produce the mature viral capsule. Both drugs are intended for use only in combination with peg-interferon alpha and ribavarin. This triple therapy may also be useful in patients that relapse after, or partially respond to, or do not respond to dual therapy.

The sustained viral response (SVR) achieved with triple therapy is higher (60%-80%) than with the dual therapy (50%-70%) described above. In addition to achieving higher SVR, patients taking direct acting antivirals are also eligible to be treated through a response guided therapy approach. This implies that patients in whom HCV-RNA reaches undetectable levels after 4 and 12 weeks of therapy need to complete only 24 total weeks of therapy instead of the standard 48 weeks. The ILLUMINATE and SPRINT-2 studies show that SVR in such patients is not affected by the duration of therapy.

Clinical end-points

The two key markers for Hepatitis B and C are viral load, which is measured by examining blood levels of HCV/HBV RNA and the level of certain liver enzymes, most significantly, hepatic transaminase ALT. The objective of treatment is that a sustained

response (SVR) is attained, that is, that there is no sign of viral RNA in the serum six months after treatment is discontinued, and that liver enzyme levels have returned to normal. Trial data are typically taken at 24 and 48 weeks. In particular for HCV, the genotype population is a crucial factor in determining significance of response.

Pipeline products

The current focus of hepatitis treatment is to develop all-oral, interferon-free combination treatment regimes. These have potential advantages given significant side effects associated with interferon which can be extremely debilitating for patients. Several companies have all-oral combinations in development including Gilead/Pharmasset (PSI-7977/ribavirin), BMS/J&J (TMC435/BMS-daclatasvir), BMS (daclatasvir/asunaprevir), Abbott/Enanta Pharmaceuticals (ABT-450, ABT-333 and ABT-072), Vertex (telaprevir/VX-222), Roche (danoprevir/mericitabine/ribavirin) and Boehringer Ingelheim (BI 201335/ BI 207127). Gilead/Pharmasset currently appear to be the most advanced and are planning to submit an NDA in the second half of 2013. Interim data from a phase II study of the PSI-7977-ribavirin combination reported results comparable to or better then existing therapies. BMS and Abbott have also reported positive results from early trials for their IFN-free oral drug combinations, in both, treatment naïve as well as relapsing patients.

It was recently discovered that a class of proteins, called cyclophilins, play an important role in HCV replication, and that this process could be blocked by cyclosporine. However, cyclosporine is usually used in organ transplants and autoimmune diseases because of its immunosuppressive effects, which limit its use in hepatitis. Hence, a novel class of drugs called cyclophilin inhibitors was developed, which aimed to reproduce the effect of binding to cyclophilins (particularly cyclophilin B), while avoiding the immunosupression associated with cyclosporine. DEB025 (alisporivir), licensed by Novartis, is a cyclophilin inhibitor in Phase IIb study, and has shown efficacy in treating HCV. This effect was enhanced when administered together with interferon. However, clinical trials of the drug are currently on hold following side effecst experienced in phase III studies.

Hepatitis B vaccines have shown high efficacy in preventing the disease (c.90%) and focus has evolved from treatment to prevention. Many countries now recommend vaccination against hepatitis B as part of their neonatal vaccination schedule. Sanofi's Hexaxim provides protection against 6 diseases including hepatitis B and is designed to improve ease of vaccination for neonates; the drug recently received a positive CHMP opinion.

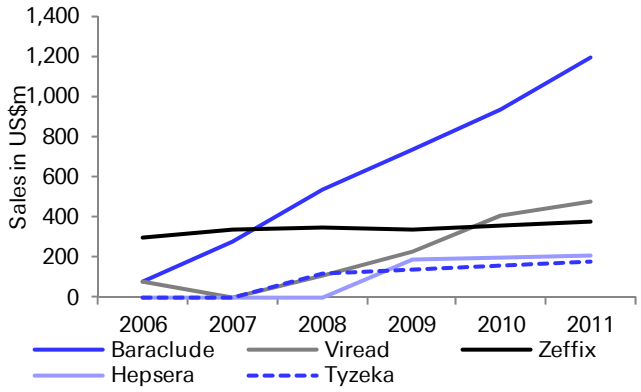
Figure 245: Selected late stage Hepatitis C pipeline

Name	Generic	Company	Class	Phase
GS-7977	GS-7977	Gilead Sciences	Nucleoside NS5B polymerase inhibitor	Phase III
TMC435	simeprevir	Johnson & Johnson	protease inhibitor	Phase III
Daclatasvir	daclatasvir	Bristol-Myers Squibb	NS5A inhibitor	Phase III
PEG-IFN-lambda	peginterferon lambda-1a	Bristol-Myers Squibb	Interferon lambda	Phase III
Asunaprevir	asunaprevir	Bristol-Myers Squibb	NS3 protease inhibitor	Phase III
MK-7009	vaniprevir	Merck & Co	protease inhibitor	Phase III
BI 201335	BI 201335	Boehringer Ingelheim	NS3/4A protease inhibitor	Phase III
SCH 900518	narlaprevir	Merck & Co	protease inhibitor	Phase III
DEB025	alisporivir	Debiopharm	Cyclophilin inhibitor	Phase III
Alferon N Injection	interferon alfa-n3	Hemispherx Biopharma	Interferon alpha	Phase III
Danoprevir	danoprevir	Roche	protease inhibitor	Phase II
RG7128	mericitabine	Roche	nucleoside NS5B polymerase inhibitor	Phase II

Source: Deutsche Bank, Company data, EvaluatePharma

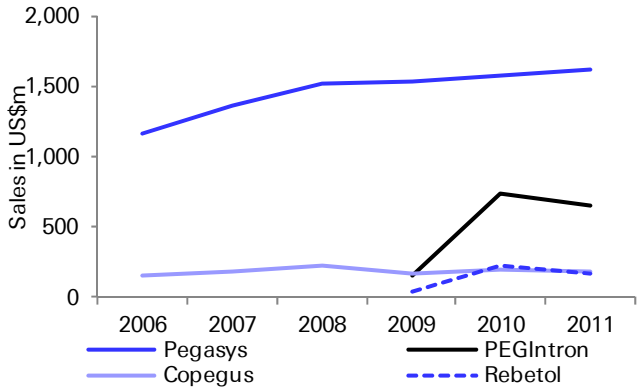
Sales

Figure 246: Sales of Hepatitis B therapies



Source: Deutsche Bank, EvaluatePharma

Figure 247: Sales of Hepatitis C therapies



Source: Deutsche Bank, EvaluatePharma

Figure 248: Sales of leading Hepatitis B therapies ($m)

Name	Company	2006	2007	2008	2009	2010	2011
Baraclude	Bristol-Myers Squibb	83	275	541	734	931	1196
Viread	Gilead Sciences	83	-	113	231	412	476
Zeffix	GlaxoSmithKline	299	336	348	340	360	380
Hepsera	GlaxoSmithKline	-	-	-	189	198	204
Tyzeka	Novartis	-	-	120	140	160	175

Source: Deutsche Bank, EvaluatePharma

Figure 249: Sales of leading Hepatitis C therapies ($m)

Name	Company	2006	2007	2008	2009	2010	2011
Pegasys	Roche	1,171	1,366	1,513	1,528	1,582	1,626
Incivek	Vertex Pharmaceuticals						951
PEGIntron	Merck & Co				149	737	657
Copegus	Roche	159	184	222	170	204	185
Rebetol	Merck				36	221	174
Victrelis	Merck						140

Source: Deutsche Bank, EvaluatePharma

Influenza

- Global sales of influenza-related drugs and vaccines totalled cS$4.8bn in 2011, down from the H1N1/H5N1 pandemic-driven $9.5bn in 2011.
- Each year, 5-15% of the population will get 'the flu'; and most recover with no ill effects.
- The leading product to treat flu is Tamiflu (Roche), but preventive vaccines dominate the category.

Influenza, or the 'flu', is an infection of the lungs caused by the highly contagious influenza virus. This virus spreads from person to person by tiny droplets produced by coughing and sneezing. Other symptoms experienced include fever, sore throat and body aches. The incidence of cases is highest in the cold season of each hemisphere (November to March for northern hemisphere, May to September for the southern hemisphere). It is estimated that between 25m and 40m people are infected each year in the US.

Physiology

The influenza virus is an RNA virus, comprising an RNA core surrounded by a lipid envelope with two glycoproteins (proteins with sugar molecules attached), called hemagglutinin (H) and neuraminidase (N), protruding from it. The nomenclature for viruses is dependent on their H and N surface antigens. For example, H1N1 refers to an influenza virus with hemagglutinin type-1 and neuraminidase type-1.

Upon inhalation of the virus, the hemagglutinin binds to sialic acid on the surface of the host's (human's) epithelial cells which line the nose, throat and lungs, prompting the cell to internalise the virus. The cell's protein-producing machinery is then used by the virus to produce multiple copies of its core and associated proteins. These are packaged into a lipid envelope made from the membrane of the infected epithelial cell. The hemagglutinin on the surface of the new virus again binds to the host cell membrane via a sialic acid bond. Finally, the neuraminidase protein cleaves the sialic acid on the host wall, releasing the mature virus and the infection spreads.

The body's immune system produces antibodies to the two viral glycoproteins when infected and protects the individual from future infections by the same virus. However, these proteins mutate easily, either as a result of 'antigenic drift' or 'antigenic shift'. Like all RNA viruses (like HIV), mutations are common in the replication process of the virus. If there is sufficiently significant mutation, such that the immune system is unable to recognise the virus, then it is unable to mount a response and a new infection occurs. This ongoing process is referred to as an antigenic drift. On the other hand, if the body is simultaneously infected with two different viruses, then there may be an exchange or mixing of surface antigens. Unlike an antigenic drift where the slow process of point mutation results in a gradual change in antigens, the mixing of proteins in an antigenic shift results in a dramatically new virus. This effect is seen more markedly in influenza A, which infects animals as well as humans, compared to influenza B and C, which mostly infect humans. Antigenic shifts are thought to be responsible for the majority of pandemics, as new strains of viruses are spontaneously created which then quickly spread through populations which have no prior immunity.

The 2009 H1N1 flu pandemic was one such pandemic. It is commonly referred to as "swine flu" because it was found to contain genes from human, swine and avian influenza A virus. It originated in Veracruz, Mexico, and was thought to be an ongoing local epidemic for a few months before it spread globally. The World Health Organization declared it a pandemic in June 2009. Fortunately, the majority of those infected only experienced normal flu symptoms, and mortality rates were not markedly higher than for a seasonal flu. However, as a precaution, governments began stockpiling neuraminidase inhibitors, and requested vaccine producers to initiate urgent production of vaccines against the H1N1 virus. By September 2009, four different vaccines were available and distributed to various countries.

Pharmacological treatment

The majority of patients recover spontaneously from influenza infections with no treatment required. However, in certain susceptible population segments, it can deteriorate to pneumonia, a more life-threatening disease requiring hospitalization. Hence, vaccination is recommended for high-risk groups such as the very young, the elderly and the immune-compromised.

Vaccines

The World Health Organization runs the Global Influenza Surveillance Network, which monitors the prevalent strains of flu and determines what strains are most likely to result in an epidemic that season. It then recommends the relevant strains to vaccine producers to be included in the vaccine for that season. Vaccines are predominantly manufactured using poultry eggs as a culture medium, a process which typically takes a number of months. The main manufacturers globally are Sanofi (c.30% market share), GlaxoSmithKline and Novartis.

As the influenza virus mutates rapidly, high-risk groups are recommended to receive the vaccine yearly to ensure that they are immunized against the most common strains for that season. However, a vaccine is unable to protect against all possible influenza variants, meaning a person who has received a vaccine may still get infected by influenza.

Neuraminidase inhibitors

Neuraminidase inhibitors block the active site of the neuraminidase protein by mimicking the host cells' sialic acid, preventing viral attachment to the host cell wall and thereby preventing the spread of viral infection. They can also be used as a prophylactic (a protective agent). The two approved drugs in this class are Roche's Tamiflu, and GlaxoSmithKline's Relenza.

Figure 250: Neuraminidase inhibitors

Name	Tamiflu	Relenza
Generic name	oseltamivir	zanamavir
Producer	Roche	GlaxoSmithKline
Sales 2011 ($)	$0.4bn	<$0.1bn
Dosing	Oral tablet	Inhaler device
US approvals	Treatment and Prophylaxis	Treatment and prophylaxis
Symptom benefit	1.3 to 1.4 day symptom reduction	1 to 1.5 day symptom reduction
Side effects	Nausea in 5% over placebo	Bronchospasm
Administration	Within 48 hours	Within 36 hours

Source: Company data

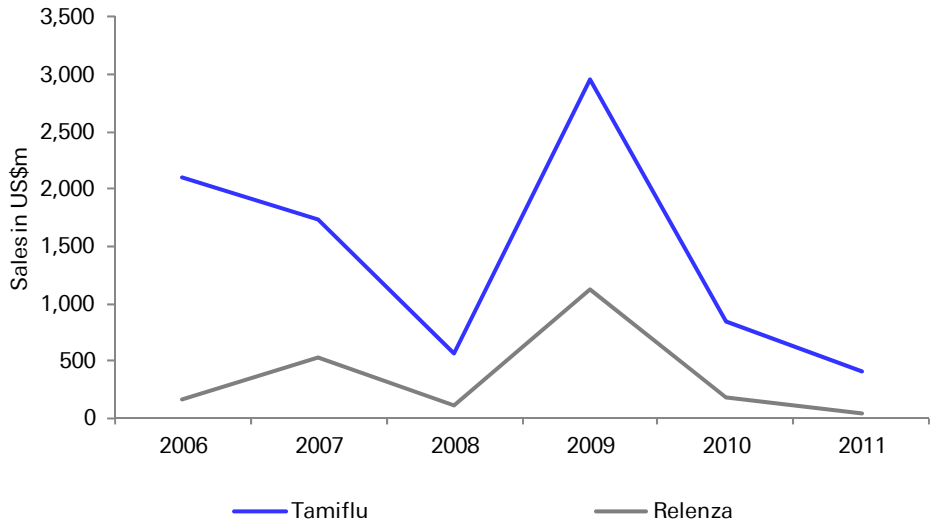
M2 inhibitors (adamantanes)

Following the intake of the influenza virus into the cell, the viral M2 membrane protein allows the entry of hydrogen ions, which starts a process of releasing the virus from its capsule for replication. The M2 inhibitor class of drugs blocks the viral M2 protein and therefore the reproduction of the virus. Amantadine, the first drug in this class, was approved by the FDA in 1966. Rimantadine was later approved in 1994. However, since the 2005-06 flu season, the CDC has recommended against the use of amantadine and rimantadine, noting that most of the prevalent influenza strains were found to be resistant to them.

Clinical end-points

The primary end-point in the treatment group is the reduction in length of symptoms, that is, how quickly patients recover from the disease. As a prophylactic, the objective of treatment is the rate of disease prevention relative to placebo.

Figure 251: Sales of leading influenza drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 252: Sales of leading influenza drugs ($m)

Name	Company	2006	2007	2008	2009	2010	2011
Tamiflu	Roche	2,097	1,740	564	2,954	840	406
Relenza	GlaxoSmithKline	168	524	106	1,127	187	43

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Introduction to CNS disorders

In recent years, scientists have made remarkable progress in our understanding of the human brain and diseases of the central nervous system (CNS). Yet, the exact workings of the brain remain poorly understood. Pathways are complex and because of the intricacy of messenger pathways and complicated feedback mechanisms, few CNS disorders are well defined. CNS disorders continue to represent a significant cause of morbidity and, as a result, represent a major source of revenues for pharmaceutical companies. In 2009, drugs for CNS disorders generated revenues totalling c.$50bn.

Over the following pages, we review the leading disorders, most significantly depression and schizophrenia. However, cause and effect are poorly understood, receptor sub-types are numerous and, as a consequence, the beginner is almost certain to be somewhat confused. Consequently, and in order to provide some type of overview, we have started this section with an overview of the principal roles played by the leading neurotransmitters found in the central nervous system.

Physiology

The basic building block of the nervous system is a single nerve or neuron. It is a single cell which conducts electrical impulses to other nerve cells, and is involved in the transmission of information (afferent or transmission from the periphery to the central nervous system, e.g. the stove is hot) and coordination of responses (efferent or transmission from the CNS to perform the desired action, e.g. remove your hand from the stove). The junction where one neuron ends and another begins is known as the synapse or synaptic cleft. When the electrical impulse reaches the end of the first neuron, it causes the release of chemicals (neurotransmitters), which diffuse across the synaptic cleft and act on the second neuron. These neurotransmitters may be excitatory (which starts or makes it easier to start a new electrical impulse), or inhibitory (which makes it harder or blocks a new electrical impulse) in nature. Each single neuron may have many other neurons acting on it, and may in turn act on many other neurons.

Although the CNS conceptually refers to the brain and the spinal cord, the pathology of most of the diseases encountered here occurs in the brain. In contrast to the spinal cord (and periphery), the brain has a wide variety of neurotransmitters, which coordinate and modulate the different activities occurring within the brain. Several of these neurotransmitters are prominent for the role they play in certain diseases. We'll go into more detail in this next section.

Leading neurotransmitters of the CNS

- **L-glutamate** is a significant excitatory transmitter in the brain. Glutamate acts upon four different categories of receptors, the most significant of which are the NMDA and AMPA receptors. It is believed to play an important role in learning/memory, but may also cause epilepsy and excitotoxicity or brain ischaemia (stroke).
- **GABA (gamma-aminobutyric acid)** is a major inhibitory transmitter in the brain. It acts on two types of receptors, GABA A and B. As an inhibitory transmitter, it plays a vital role in dampening activity in the brain. Drugs such as benzodiazapine sedatives and barbiturates act by enhancing its receptor

binding, causing sedation and tranquillity. GABA agonists are also used as anti-convulsants and anti-epileptics.

- **Noradrenaline (norepinephrine)** has both inhibitory and excitatory effects. As with many neurotransmitters, its exact role is unclear. Among other effects, it is believed to increase wakefulness and alertness. It has been suggested that a functional deficiency of noradrenaline leads to depression, while an excess may result in mania. Outside of the brain, noradrenaline also plays a key role in the regulation of blood pressure.
- **Dopamine** is a neurotransmitter, as well as being a precursor of noradrenaline. Among other functions, it plays an important role in motor function (movement) and mood. It is broken down by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). Dopamine acts on two main receptor classes, entitled D1 and D2 type. Given its importance in motor control, it plays a key role in Parkinson's disease, which causes patients to suffer from a deficiency of dopamine. Conversely, excess levels of dopamine may play a role in schizophrenia. Dopamine is associated with vomiting (emesis). Thus, nearly all dopamine receptor agonists (stimulators) cause vomiting and nausea as a side effect, while dopamine antagonists (depressors) may potentially be anti-emetics.
- **Serotonin (5-hydroxytryptamine or 5HT)** is associated with wakefulness, mood, hallucinations, sleep and behaviour. Following its release, it action is terminated largely by neuronal uptake (reabsorbed by the releasing neuron). This reuptake may be inhibited by specific serotonin reuptake inhibitors (SSRIs), an important class of antidepressant, which results in an increased concentration and a prolonged duration of action at the synaptic cleft. As with dopamine, serotonin is also degraded by MAO.
- **Acetylcholine** plays an important role in the CNS. It has a largely excitatory role, acting on two classes of receptors described as muscarinic and nicotinic. The main functions ascribed to cholinergic pathways are related to arousal and learning. As such, certain neurodegenerative disorders, such as Parkinson's and Alzheimer's disease, are associated with abnormalities in cholinergic pathways. Muscarinic receptors act to block acetylcholine release and mediate the main behavioural effects associated with acetylcholine (learning and memory). Antagonism or blockage of muscarinc receptors has been noted to lead to amnesia (forgetfulness). Separately, activation of nicotinic receptors have also been observed to potentiate the release of other excitatory transmitters, such as dopamine and glutamate.

Figure 253: Summary of major CNS neurotransmitters

Neurotransmitter	Receptors	Functional role	Disease involvement	Drug types	Key enzymes
Glutamate	NMDA, AMPA	Excitatory	Stroke, epilepsy	None significant	GABA aminotransferase
GABA	GABA Types A & B	Dampens CNS activity	Epilepsy, sedation	Benzodiazepines, barbiturates	GAD (creation), GABA transaminase
Serotonin (5-HT)	5HT 1-4	Hallucinations, mood, alertness	Depression, anxiety	SSRIs, TCAs, MAOIs	MAO (degrades)
Noradrenaline	Beta-adreno receptors	Alertness,	Depression, anxiety	SSRIs, TCAs	Created by DOPA decarboxylase
Dopamine	D1 and D2	Motor control, mood	Parkinson's, schizophrenia	Dopamine agonists, antagonists,	MAO and COMT degrade
Acetylcholine	Muscarinic and nicotinic	Learning, memory	Alzheimer's	Cholinesterase inhibitors	Acetylcholinesterase (degrades)

Source: compiled by Deutsche Bank

Schizophrenia

- Global sales of drugs for schizophrenia totalled c.$21bn in 2011, (7% CAGR over 2006-11).
- Around 1% of the population worldwide is affected and it is a major source of morbidity for patients.
- Leading products include Seroquel (AstraZeneca), Abilify (Bristol-Myers Squibb/Otsuka) and Zyprexa (Eli Lilly).

Schizophrenia is a disorder of the mind that is believed to arise from a neurochemical imbalance in the brain. Derived from the Greek origin meaning 'split mind,' it is a relatively common condition affecting approximately 1% of the population at some point in their lives. Some 15-30 new cases are diagnosed per 100,000 people annually. It develops mainly in young people, affecting men and women equally, though the symptoms seem to appear earlier in males (generally between the ages of 15 and 24). Unfortunately, patients with this condition often become isolated from society, which may lead to attempts at suicide. The development of drugs with fewer side effects has driven strong growth of the market in recent years.

The symptoms of schizophrenia can be broadly divided into positive and negative symptoms. Positive refers to symptoms which are found in patients with schizophrenia, but are not found in normal people. Negative symptoms refer to the paucity or loss of certain behaviours which are found in normal people, but are not found in patients with schizophrenia. Negative symptoms may co-exist with positive symptoms from the start, or may develop later. Diagnosis of Schizophrenia in the latest Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) recognizes that in addition to symptoms, patients also exhibit signs of deterioration in work and/or social setting, and that these symptoms should be present for at least six months.

Figure 254: Schizophrenia – positive and negative symptoms

Positive symptoms	Negative symptoms
Hallucinations (voices)	Apathy
Delusions (often paranoid)	Flattening of emotions
Thought disturbances (irrational)	Withdrawal from society

Source: Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV)

While the cause of schizophrenia remains unclear, it is believed to involve a combination of genetic and environmental factors. As such, it is seen as a neurodevelopmental disorder rather than a neurodegenerative one (for example, Alzheimer's and Parkinson's). In first-degree relatives, the incidence of schizophrenia is 10%, strongly supporting a hereditary and thus genetic disposition to the disease.

Physiology

As with other CNS disorders, an accurate physiology of schizophrenia is not known. However, pharmacological evidence suggests that it is associated with dopamine overactivity, as dopamine agonists have been seen to induce schizophrenia, while dopamine antagonists have controlled it. There are two main classes of dopamine receptors in the brain, classed as D1 and D2, and the dopamine receptors relevant to the actions of the anti-psychotic drugs mainly belong to the D2 family (namely D2, D3 and D4). Even within the D2 family, the receptor function is also dependent on its

location within the brain. Consequently, side effects with drug treatment are common. The 'typical' anti-psychotics act by inhibiting the action of dopamine on D2 receptors in the mesolimbic area of the brain, with a favourable impact on the positive symptoms of schizophrenia (but little effect on the negative). However, their impact on D1 and D2 receptors elsewhere has meant that most of the 'typical' anti-psychotics have distinct side effects, which broadly fall into three categories:

- **Extrapyramidal side effects (EPS).** These are the most problematic effects of treatment, consisting of involuntary movements (muscle spasms, twitching, shaking), which often resemble the symptoms of Parkinson's disease (a disease characterised by a deficiency of dopamine).
- **The release of prolactin**. Because dopamine plays a role in inhibiting the secretion of this hormone, dopamine antagonists may produce an increase in plasma prolactin levels. This results in breast swelling, pain and lactation in both men and women.
- **Autonomic side effects**. Effects on receptors in the periphery can cause blurred vision, increased pressure in the eye, urinary retention and other side effects.

Beyond dopamine, the observation that the recreational drug LSD can induce hallucinations by acting on 5HT receptors has led to the development of 'atypical' anti-psychotic therapy. Serotonin (or 5HT) is known to modulate dopaminergic pathways, and by inhibiting 5HT, side effects associated with the earlier or 'typical' pharmacological treatments have been reduced. Additionally, it has been suggested that by blocking 5HT, the negative symptoms associated with schizophrenia may also be reduced. However, as a class, studies have found an increased risk of weight gain and diabetes associated with taking atypical anti-psychotics. This resulted in lawsuits surrounding a number of drugs, where patients alleged that they were not warned of these side effects.

Pharmacological treatment

As pharmacological treatment has developed, it has led to the emergence of two distinct classes of drugs – 'typical' and 'atypical' anti-psychotics, as above. The distinction between the two is not well-defined, but rests on differences in the incidence of EPS side effects, efficacy against hard-to-treat patients and efficacy against negative symptoms. The typical anti-psychotics represent earlier drugs discovered and used in therapy. They generally act by inhibiting the action of dopamine in the brain and work well against positive symptoms. However, their effect on the negative symptoms associated with schizophrenia is often more muted and side effects, particularly EPS, tend to be significant. Early drugs in this class include the phenothiazines (for example, chlorpromazine). These were subsequently displaced following the 1958 discovery of haloperidol, which showed a much-reduced incidence of extrapyramidal side effects. It is of note that haloperidol remains an important benchmark when assessing the benefits of new drugs in development.

Figure 255: Classes of schizophrenia treatment

Typical	Atypical
chlorpromazine	clozapine (Clozaril)
sulpiride (Dogmatil)	risperidone (Risperdal)
haloperidol (Haldol)	olanzapine (Zyprexa)
	quetiapine (Seroquel)
	ziprasidone (Geodon)
	apriprazole (Abilify)

Source: Deutsche Bank

More recently, the development of the atypical anti-psychotics has helped to drive the dramatic growth of the overall class, and it is these drugs that dominate today's markets. While side effects remain a key negative, their incidence has been much reduced, while containment of both positive and negative features of schizophrenia has been improved. However, sales of this class are expected to decline in the future as top-selling drugs Zyprexa, Seroquel and Risperdal lose patent protection in the coming years.

Figure 256: Leading atypical anti-psychotics

Name	Generic	Company	2011 sales ($)
Seroquel	quetiapine fumarate	AstraZeneca/Astellas Pharma	$6.2bn
Abilify	aripiprazole	Otsuka Holdings	$5.2bn
Zyprexa/Zelprexa Relprevv	olanzapine	Eli Lilly	$4.6bn
Risperdal/Risperdal Consta	risperidone	Johnson & Johnson	$2.1bn
Geodon	ziprasidone hydrochloride	Pfizer	$1.bn
Invega/Invega Sustenna	paliperidone	Johnson & Johnson	$0.9bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Clozaril

The first atypical anti-psychotic, Clozaril, is now off-patent. The drug, associated with serious blood disorder agranulocytosis, was withdrawn for a period of time. It was later re-introduced when it was found that it had a high efficacy, especially in patients who were resistant to other anti-psychotics. Clozaril has now been approved for treatment-resistant cases of schizophrenia. However, regular blood tests are required.

Zyprexa

Launched in 1996, Zyprexa has higher selectivity for 5HT than for dopaminergic and muscarinic receptors. It has good activity against both positive and negative symptoms of schizophrenia, needs to be taken once a day, and has fewer EPS side effects than haloperidol. However, it causes weight gain in some patients and may increase the risk of developing diabetes. In 2009, an extended release formulation, Zyprexa Relprevv, was approved which allowed it to be given as an injection with effects lasting up to four weeks.

Risperdal

Despite its 1994 US launch, a higher incidence of EPS (particularly at higher dosages) and the need for dose titration (gradual increases in dosage to find the appropriate level) have caused Risperdal to lose ground to newer entrants. Taken once a day, the drug acts on both dopaminergic and 5HT receptors, treating the positive and negative effects of schizophrenia. In addition to the EPS, it is also associated with weight gain, diabetes and hyperprolactinemia. It now comes in a long-acting formulation, Risperdal Consta, which can be given once every fortnight, and is seen by physicians as a choice for patients with compliance problems.

Seroquel

Although Seroquel got off to a slow start following its US launch in 1997, it has since steadily gained market share. Seroquel has been successful due to its low incidence of EPS. It is also effective against positive and negative symptoms, and does not appear to induce as much weight gain. The main side effects associated with Seroquel are sedation, Diabetes and weight gain. Seroquel has also been approved as a treatment for bipolar disorders (also knows as manic depression), gaining a large proportion of sales from this indication.

Geodon

Launched in 2001 after long delays at the FDA, Geodon is a novel serotonin and dopamine antagonist that does not induce weight gain. However, its uptake has been slow due to concerns about its effect on the heart (QT prolongation) that emerged during clinical trials and unproven efficacy relative to other class products.

Abilify

Abilify (aripiprazole), launched in late 2002, benefits from once-daily dosing, minimal EPS side effects (although these may rise at higher doses) and limited weight gain. It is a partial dopamine and serotonin agonist, thus treating the positive and negative effects of schizophrenia.

Invega

Approved in 2006, Invega is available as a once-daily oral dose, and a once-monthly injection. Invega is the active metabolite of Risperidal. Hence it has a similar side effect profile and efficacy, but benefits from a more convenient dosing schedule.

Sycrest/ Saphris

Sycrest (asenapine) was first approved in 2009 and is available as sublingual tablets. It is approved in the EU for treatment of manic episodes associated with bipolar disorder while in the US for it is also approved for schizophrenia. Although similar to Zyprexa in efficacy for treatment of bipolar disorder, Sycrest had a lower incidence of associated weight gain.

Figure 257: Comparison of leading anti-psychotics

	Zyprexa	Seroquel	Abilify	Risperdal	Geodon
Generic	olanzapine	quetiapine	aripiprazole	risperdone	ziprasidone
Company	Eli Lilly	AstraZeneca	Bristol-Myers	Johnson & Johnson	Pfizer
US launch	1996	1997	2002	1994	2001
Dosing	Once daily	Twice daily	Once daily	Twice daily	Twice daily
Prominent EPS effects	No	No	No (except at higher doses)	Yes	No
Hyperprolactin (linked to sexual dysfunction)	Yes	No	No	Yes	Yes
Weight Gain	Yes	No	No	Yes	No
Boxed warning	Boxed warning on dementia-related psychosis in elderly and suicidal thoughts	Boxed warning on dementia-related psychosis in elderly and suicidal thoughts	Boxed warning on dementia-related psychosis in elderly and suicidal thoughts	Boxed warning on dementia-related psychosis in elderly	Boxed warning on dementia-related psychosis in elderly
Other	Adverse lipid effects	Possible risk of cataracts	Increased risk of nausea		QT prolongation

Source: Company data

Clinical end-points

Key to clinical trials is the impact of any new molecule on the positive and negative symptoms of schizophrenia, together with a favourable side effect profile. These are assessed subjectively by clinicians and patients, and marked according to the Positive and Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS). Controlled trials measuring the performance of the new entity against haloperidol (and perhaps olanzapine and risperidone) as a comparison are usually undertaken to show a favourable outcome or non-inferiority. However, given the nature and objectivity of schizophrenia, programmes are typically subject to a number of clinical trials in an attempt to navigate high rate of failes studies.

Pipeline products

Generic competition from the patent expiry of top blockbuster drugs such as Zyprexa, Seroquel and Abilify will likely place a heavy burden on newer drugs to differentiate themselves in terms of efficacy or a more tolerable side effect profile in order to gain significant market share. However, there are still several new atypical anti-psychotics in development and given the chronic nature of this condition, we believe a sizable opportunity still exists for new drugs with a differentiated profile.

Forest Laboratories/Gedeon Richter's cariprazine is a D2/D3 and 5HT antagonists, which binds preferentially to Dopamine type-3 receptors, which was hoped to results in a lower incidence of EPS. The company announced three positive Phase III trials in schizophrenia (and a further three positive Phase III trials in bipolar mania). However, despite the drug's mechanism of action, patients experienced a significant number of side effects, including akathesia, insomnia and weight gain, which may negatively impact the drug's prospects vs atypical antipsychotics which are already on the market.

Lundbeck/Otsuka have filed for approval of an aripiprazole depot formulation, which permits the convenience of once-a-month dosing. In July 2012, the FDA issued a CRL in reponse to the NDA, citing issues with a third-party supplier. A filing for EMA approval is expected in 2H12.

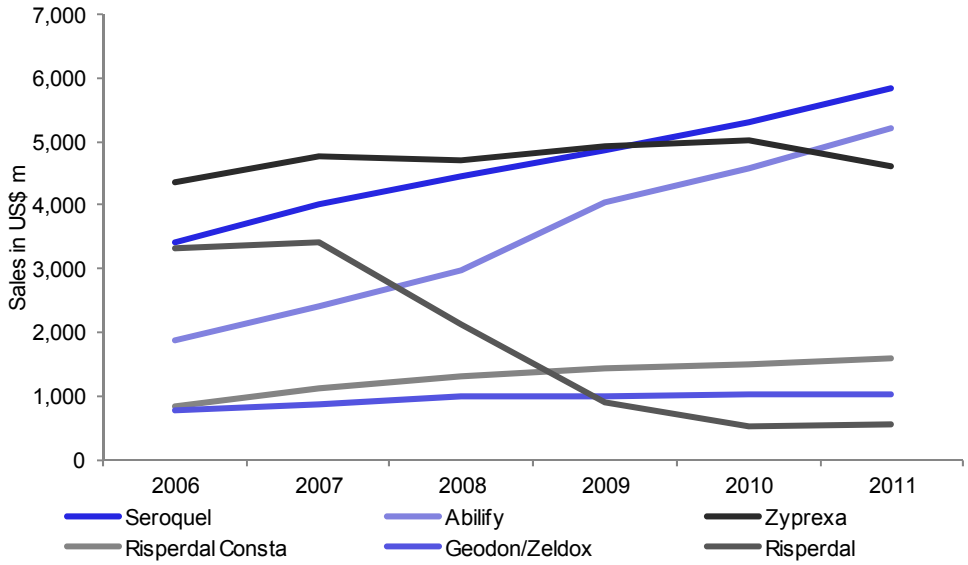
Figure 258: Selected late-stage pipeline anti-psychotics

Name	Generic	Class	Company	Stage
SM-13496	lurasidone	5-HT2A (serotonin) & D2 antagonist	Dainippon Sumitomo Pharma	Filed
Aripiprazole depot	Aripiprazole	5-HT1A & D2 partial agonist & 5-HT2 antagonist	Lundbeck/ Otsuka	Filed
RGH-188	cariprazine	Dopamine D1 & D2 antagonist	Forest Laboratories /Gedeon Richter	Phase III

Source: Company data, Deutsche Bank

Sales

Figure 259: Sales of leading drugs for schizophrenia



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 260: Sales of leading drugs for schizophrenia ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Seroquel	AstraZeneca	3,416	4,027	4,452	4,866	5,302	5,828
Abilify	Otsuka Holdings	1,889	2,405	2,967	4,039	4,593	5,216
Zyprexa	Eli Lilly	4,364	4,761	4,696	4,916	5,026	4,622
Risperdal Consta	Johnson & Johnson	845	1,128	1,309	1,425	1,500	1,583
Geodon/Zeldox	Pfizer	758	854	1,007	1,002	1,027	1,022
Risperdal	Johnson & Johnson	3,338	3,420	2,126	899	527	542

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Parkinson's disease

- Global sales of drugs treating Parkinson's disease totalled c.$2.8bn in 2011.
- Limited effective long-term treatments are available.
- Leading products include Comtan (Novartis) and Mirapex (Boehringer Ingelheim).

Parkinson's disease is the second-most common adult-onset neurodegenerative disease. It affects about 4m people worldwide, or roughly 0.5-3.0% of people over the age of 65. It is a progressive disorder of movement that occurs mainly in the elderly, the classic signs of which are tremor, rigidity and the paucity of voluntary movements. The disease shows no hereditary tendency, but is often preceded by stroke or viral infection and appears to be more prevalent in men than in women. Memory impairment and cognitive dysfunction are rarely encountered in the early stages of Parkinson's disease, though 25-30% of sufferers eventually develop some form of dementia. Depression is also a commonly associated feature.

Physiology

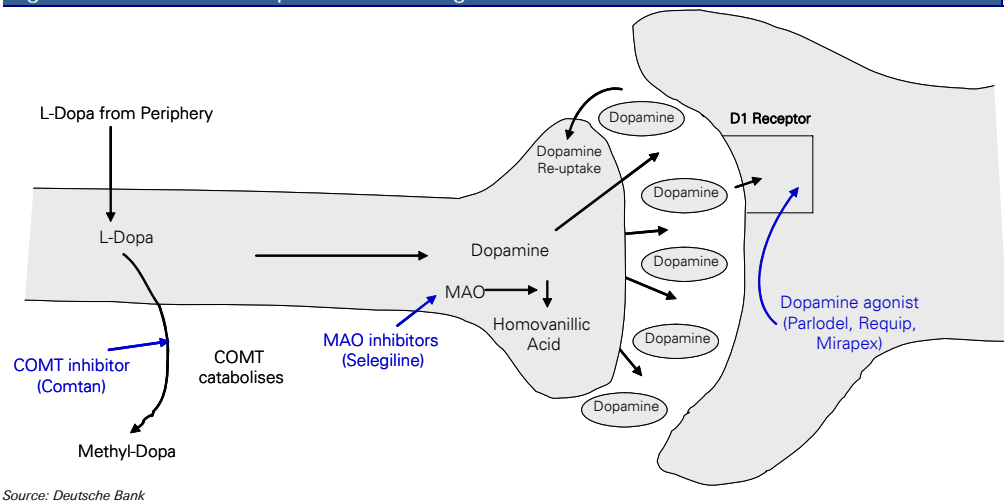
The main feature of Parkinson's disease is the progressive destruction of dopamine-producing cells in the substantia nigra, a part of the brain associated with motor control. Dopamine plays a key role in motor control (movement), both directly and by controlling (depressing) the level of acetylcholine released in other parts of the brain. Post-mortem studies have revealed that the symptoms appear once dopamine levels in this part of the brain reaches 20-50% of normal levels, or when 60-80% of the dopaminergic neurons in the substantia nigra have been destroyed. Their loss results in an unbalanced stimulation of pathways which inhibit movement, leading to the rigidity and hypokinesia (reduced voluntary movement) characteristic of the disease. The loss of inhibition also leads to a tremor at rest, which is one of the most common features of the condition. It is also important to note that the diagnosis of Parkinson's disease is made clinically based upon medical history and physical examination as there is currently no laboratory test which is able to definitively establish a diagnosis.

Pharmacological treatment

Given that the apparent cause of Parkinson's disease is a lack of dopamine in the brain, current pharmacological treatment is aimed at increasing dopamine levels, either directly or through slowing its metabolism in the brain.

Traditionally, the first-line treatment is Levodopa (L-dopa), a dopamine precursor which crosses the blood-brain barrier. 95% of L-dopa is metabolised before it reaches the brain, hence, L-dopa therapy is nearly always combined with a decarboxylase inhibitor, which blocks the metabolism of L-dopa in the body. However, as the decarboxylase inhibitor is unable to cross the blood-brain barrier, L-dopa is rapidly broken down once it is in the CNS. Unfortunately, while L-dopa can be seen to provide immediate benefit to patients in the early stages of their disease, its effectiveness declines as the disease progresses. The drug also has significant, albeit slowly developing side effects, such as involuntary writhing movements, which tend to develop within two years of treatment, and sudden rigidity, which is believed to arise as the brain's ability to store the administered dopamine deteriorates. Typically, after five years of treatment, more than 60% of patients are little better than they were at the inception of treatment.

Figure 261: Action of dopamine and drugs to treat Parkinson's



Source: Deutsche Bank

Beyond direct treatment with L-dopa, current pharmacological treatments include dopamine agonists and drugs which inhibit the enzymes that degrade dopamine. These are typically used in combination with L-dopa and include inhibitors of both monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT). However, no treatment has as yet shown itself capable of fully or permanently restoring motor function. Importantly, dopamine agonists can be given as monotherapy before initiating L-dopa with the hope of extending the effectiveness of L-dopa therapy. Equally, COMT inhibitors also extend the effectiveness of L-dopa and may reduce side effects.

As a class, few drugs have significant sales, which largely reflect the maturity of current drugs and the absence of any dramatic advances in medication. Many of the currently available drugs are off-patent.

Figure 262: Leading drugs treating Parkinson's disease

Name	Generic	Company	2011 sales ($)
Comtan	entacapone	Novartis	$0.6bn
Mirapex	pramipexole dihydrochloride	Boehringer Ingelheim	$0.5bn
Azilect	rasagiline mesylate	Lundbeck/Teva	$0.4bn
Madopar	benserazide; levodopa	Roche	$0.3bn
Requip XL 24-Hour	ropinirole hydrochloride	GlaxoSmithKline	$0.2bn
Neupro	rotigotine	UCB	$0.1bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Pipeline products

Given the lack of success in treating Parkinson's disease, it is unfortunate that there has been a dearth of new drugs in recent years. With the wide variety of dopa agonists and MAO/COMT inhibitors in the market, it has become harder for new products to differentiate themselves from older generic therapies. Prominent drugs in the pipeline include Newron's safinamide, an alpha-aminoamide which is being developed as an add-on therapy to dopamine agonists or levodopa in patients with early or mid-to-late stage Parkinson's disease. Rights to the compound were returned to Newron by Merck KGaA in April 2012. Newron has announced the results from the Phase III MOTION and SETTLE studies were consistent with the efficacy and safety reported in previous Phase II/III studies and that drug was generally well tolerated. Full data will be presented at

upcoming scientific meetings, which will provide an indication of the future of this drug.

Separately, UCB has partnered with Biotie Therapies to develop SYN-115, an oral inhibitor of adenosine 2A (A2A) receptor. The blockage of adenosine at the A2A receptor is believed to results in a potentiation of the effect of dopamine and an inhibition of the effect of glutamate, which will hopefully resulst in a normalization of motor function while having a lower incidence of side effects. We note that A2A antagonists have been looked at previously in Parkinson's with no obvious success to date (e.g. Kyowa Hakko's istradefylline/KW-6002). In April 2011, Biotie commenced a randomized, double-blind, placebo-controlled Phase 2b study that will evaluate four doses of SYN115 versus placebo as adjunctive therapy in 400 levodopa-treated PD patients with end of dose wearing off and results will be announced in 1H 2013.

GlaxoSmithKline and Partner Impax have filed for regulatory approval of IPX066, an extended-release formulation of carbidopa-levodopa, following positive data announced from the Phase III ADVANCED-PD and ASCEND-PD studies. In ASCEND-PD, IPX066 resulted in a reduction in "off time" of 34% from baseline vs. a 10% decrease for standard therapy.

There are also several companies which are developing drugs for the treatment of side effects or associated conditions.

Chelsea Therapeutics is continuing its late-stage study on Northera, a drug which is being developed for the treatment of neurogenic orthostatic hypotension in patients with Parkinson's disease. The company received a complete response letter following an FDA review (despite a 7-4 for approval from the Advisory Committee with 1 abstention and 1 non-vite), citing concerns around the drug's safety and lack of long-term efficacy data. The company is continuing clinical trials and plans to resubmit a response in 1Q 2013.

Adamas Pharma is developing an extended formulation of an old drug, amantadine, for the treatment of levodopa-induced dyskinesias. This is currently in Phase II/III study and is expected to complete in Feb 2013. We note Novartis is also developing a compound, AFQ056, being studied in this indication with phase II results expected in 2012.

Acadia Pharma is developing Pimavanserin, a selective blocker of 5-HT2A, for the treatment of Parkinson's disease psychosis. This is a debilitating condition for patients with Parkinson's disease, whose exact cause is not clear. We note a previous Phase III trial in 2009 failed to produce significant results, purportedly due to a high response rate in the placebo group. Acadia has since regained all rights to the drug (previously licensed to Biovail, which was acquired by Valeant) and has embarked on a second Phase III trial, which is expected to complete in July 2012.

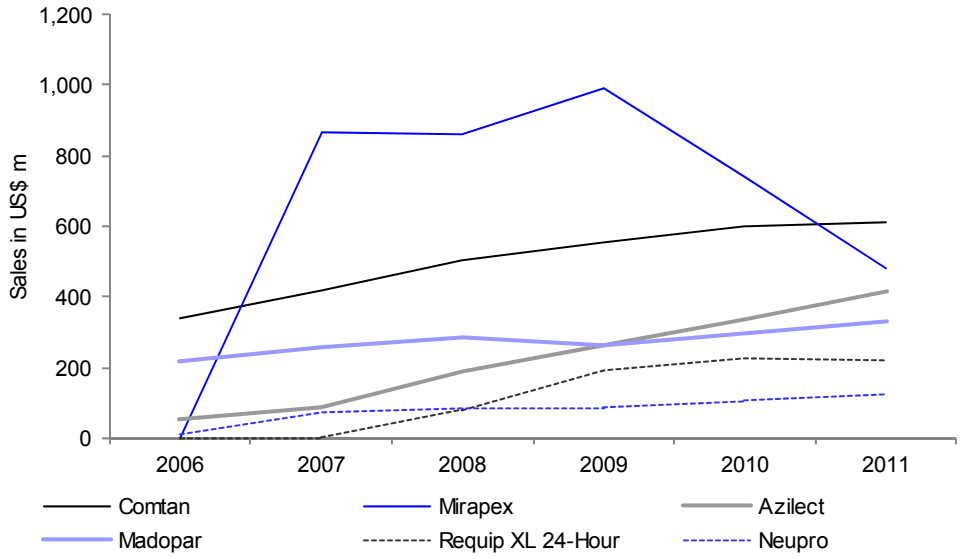
Figure 263: Selected late-stage anti-Parkinson's drugs

Name	Generic	Class	Company	Stage
IPX066	Levodopa; Carbidopa	dopamine agonist	GlaxoSmithKline/Impax	III
safinamide	alpha-aminoamide	MAO-B inhibitor	Newron	III
Pimavanserin		5-HT2A receptor antagonist	Acadia Pharm	III
Nurelin (ADS-5102)	amantadine ER	NMDA antagonist	Adamas Pharma	III
Northera	droxidopa	norepinephrine precursor	Chelsea Therapeutics	III
SYN-115	tozadenant	A2A antagonist	UCB/Biotie Therapies	IIb
AFQ056		(mGluR5 antagonist	Novartis	II

Source: Company data

Sales

Figure 264: Sales of leading drugs for Parkinson's disease



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 265: Sales of leading drugs for Parkinson's disease ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Comtan	Novartis	339	420	502	554	600	614
Mirapex	Boehringer Ingelheim		865	862	992	744	479
Azilect	Lundbeck/Teva	56	85	190	261	334	418
Madopar	Roche	219	259	288	264	296	332
Requip XL	GlaxoSmithKline		-	80	193	229	223
Neupro	UCB	10	71	85	85	105	125

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Alzheimer's disease

- Global sales of drugs for Alzheimer's disease totalled c.$6.2n in 2011. Market set to shrink as blockbuster Aricept loses patent protection.
- The condition affects 10% of the over-65 population, with an estimated 35m people afflicted worldwide.
- Leading current products include Aricept (Pfizer/Eisai), Namenda (Forest) and Exelon (Novartis).

Alzheimer's disease (AD), first characterised by Alois Alzheimer in 1907, is a gradual progressive dementia affecting cognition and behaviour. It is characterised by a loss of short-term memory as well as deterioration in behaviour and intellectual performance. The exact physiology is unknown, and no cure exists. Alzheimer's is generally thought of as a disease of old age because most symptomatic cases present after the age of 65, albeit the underlying disease may be developing from a younger age. The disease affects 10% of people over the age of 65 and almost 50% of those aged 85 and over.

Physiology

Alzheimer's dementia is characterized by a progressive physical destruction of the brain. As the disease progresses, 'plaques' and 'tangles' develop in the structure of the brain, which lead to death of cells in the brain and progressive loss of synaptic function. As Alzheimer's is a progressive disease, these changes occur gradually over time and symptoms slowly become more severe.

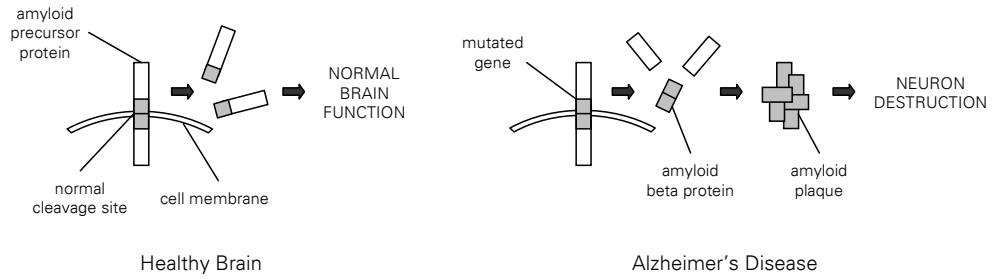
The disease is associated with shrinkage of brain tissue and localised loss of neurons (nerve fibres) in certain parts of the brain. Two microscopic features are characteristic of the disease, namely, the existence of extracellular 'amyloid' proteins, which are similar in nature to starch and which form plaque around brain neurons, and intra-neuronal meshes of filaments (tau proteins), called neurofibrillary tangles. Various theories have been put forward surrounding the role these proteins play in the pathogenesis of Alzheimer's disease.

One theory, the "amyloid hypothesis", is based on a glycoprotein called amyloid precursor protein (APP) which is cleaved by the enzymes gamma- and beta-secretase in the brains of normal individuals, which is thought to aid memory function. The theory holds that abnormal processing of APP gives rise to amyloid proteins (called beta amyloid proteins), which accumulate as extracellular plaques in the brain. These plaques are thought to play a role in the destruction of brain neurons, either directly or as a result of an immune response to the plaque. The main arguments that support the amyloid accumulation hypothesis are based on the association of beta amyloid plaques with disease and the fact that mutations or polymorphisms in at least four genes have been shown to cause or dramatically increase the risk for Alzheimer's disease and all four have been shown to result in amyloid formation in the brain. Other genes have been associated with reduced amyloid clearance. However, the amyloid hypothesis is by no means proven as the major driving factor of the disease and there are several alternative hypotheses.

Another theory holds that it may in fact be the soluble forms of beta amyloid which are the culprit. Laboratory experiments with genetically engineered mice have pointed to soluble beta amyloid as a possible primary neurotoxic component. Some leading

neurologists have further suggested that plaques may be the body's way of trapping and neutralizing these oligomers.

Figure 266: Plaque formation in Alzheimer's disease



Source: Dipiro, Talbert, Uee, Matzke, Wells and Pose, Deutsche Bank

Pharmacological treatment

Acetylcholine is believed to play a role in learning and short-term memory. In patients with Alzheimer's disease, the concentration of acetylcholine and the number of neurons which produce acetylcholine are reduced. Hence, drug therapy has focused on increasing the concentration of acetylcholine in the brain to enhance the function of the remaining neurons. This is usually achieved by inhibiting the breakdown of acetylcholine by the enzyme acetylcholinesterase. Although this does not cure the disease, it has been observed to slow the rate of symptom deterioration in Alzheimer's patients by 6-12 months.

To date, three drugs which inhibit acetylcholinesterase (and hence increase acetylcholine levels) have been approved for use in Alzheimer's, as described in Figure 267 below.

Figure 267: Leading acetylcholinesterase inhibitors

Name	Aricept	Exelon patch	Reminyl/Razadyne
Generic	donepezil	rivastigmine	galantamine
Manufacturer	Pfizer/Eisai	Novartis	Johnson & Johnson/Shire
Sales 2011 ($)	$2.4bn	$1.1bn	$0.4bn
Side effects	Nausea, vomiting, diarrhoea	Nausea, vomiting, diarrhoea, weight loss	Nausea, vomiting, diarrhoea
Indication	Mild to Severe AD	Mild to Moderate AD	Mild to Moderate AD
Dosing	Once-a-day	Twice-a-day	Twice-a-day

Source: Company data, Deutsche Bank

Differing from acetylcholinesterase inhibitors, Forest Laboratories' Namenda is an NMDA receptor antagonist which has neuro-protective effects in patients with Alzheimer's disease. Excessive stimulation of NMDA receptors by glutamate is thought to contribute to cell death in the brain of patients with Alzheimer's disease. Therefore, Namenda/Ebixa inhibits the stimulation of NMDA receptors by glutamate, thereby protecting the brain. Because of its unique mechanism of action, it may be given in combination with acetylcholinesterase inhibitors. The drug is approved for the treatment of moderate to severe AD, and an extended release version, Namenda XR, received FDA marketing approval in June 2010.

Figure 268: Leading NMDA antagonist

Name	Namenda/Ebixa
Generic	memantine
Manufacturer	Forest Labs/Lundbeck
Sales 2011 ($)	$1.9bn
Side effects	Well-tolerated
Indication	Moderate to Severe AD
Dosing	Twice a day

Source: Company data, Deutsche Bank

Clinical end-points

The end-points of trials assessing the efficacy of new molecules in Alzheimer's disease rest heavily on the subjective assessment of clinicians, as is the case with other CNS diseases. Various structured interview-based scales measuring efficacy against placebo exist. Most significant among these are the Alzheimer's Disease Assessment Scale (ADAS), Disability Assessment Scale for Dementia (DAD) and the Clinicians' Interview-Based Impression of Change (CIBIC).

Pipeline products

Several candidate compounds are in development which target beta amyloid accumulation. These aim to either increase clearance of B-amyloid plaques (such as anti beta amyloid antibodies or vaccines), or through inhibition of gamma and beta secretase enzymes, prevent beta amyloid formation. Initial trials with amyloid targeting therapies have thus far been inconclusive, with five drugs targeting beta amyloid thus far failing to show a meaningful clinical benefit - Elan's amyloid beta vaccine AN1792, Myriad/Lundbeck's Tarenflurbil (a modulator of Gamma-secretase), Neuromed's Alzhemed (believed to prevent beta amyloid aggregation), Eli Lilly's semagacestat and most recently, Pfizer/Johnson & Johnson/Elan's bapineuzumab.

Eli Lilly's biologic compound in development, named solanezumab, is a humanised Beta amyloid antibody. Solanezumab is believed to bind only to soluble amyloid beta and not directly to plaque amyloid. This may account for the differences in adverse event profile to bapineuzumab. In two pivotal Phase III studies, solanezumab failed to meet the primary endpoints (cognitive and functional) in patients with mild to moderate Alzheimer's disease. However, the company reported that a pre-specified analysis of pooled data across both studies showed a statistical significant slowing of cognitive decline in the overall population of patients. Subgroup analyses of pooled data also showed a significant slowing of cognitive decline in patients with mild Alzheimer's disease but not in patients with moderate disase. The future of this compound is now in doubt as the company will meet with regulators to discuss the results.

Finally, Baxter is conducting two Phase III studies exploring the use of IVIG in the treatment of mild to moderate Alzheimer's disease. Interest in the use of IVIG in Alzheimer's disease was first stirred in the early 2000s when it was observed that sufferers had lower levels of circulating antibodies against amyloid, a protein that is found in plaques in the brains of patients with the disease. It was also reported that IVIG was found to contain very high concentrations (c.15x compared to normal human plasma) of anti-amyloid antibodies. The Phase II study showed that treatment with IVIG resulted in a slowing in deterioration of mental function, as measured Clinical Global Impression of Change (CGIC) and Alzheimer's disease Assessment Scale-Cognitive

(ADAS-Cog). Two Phase III studies are underway and Baxter expects results to report results from the first study in mid-2013.

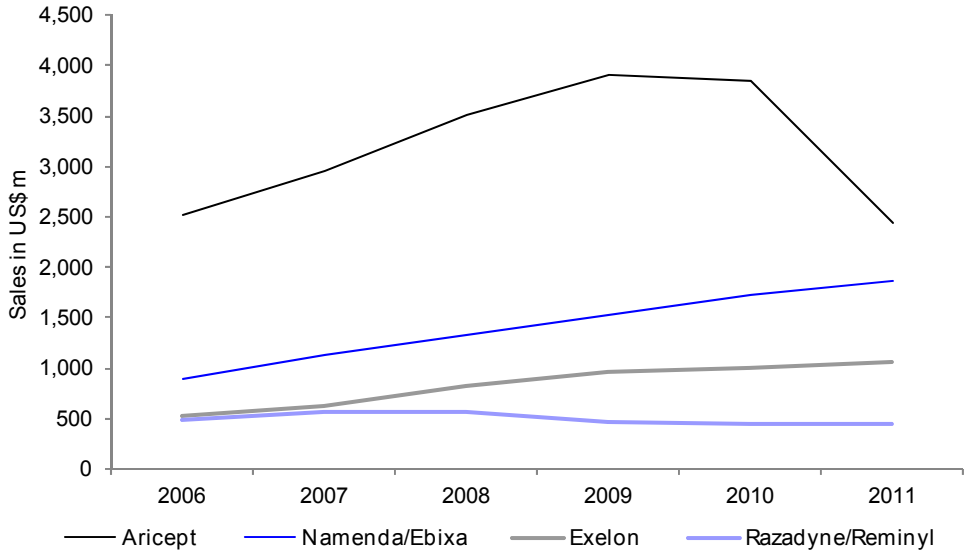
Figure 269: Selected late-stage drugs for Alzheimer's disease

Name	Class	Company	Stage
solanezumab	Anti-beta amyloid mAb	Eli Lilly	Phase III
Gammagard	IVIG	Baxter	Phase III

Source: Company data

Sales

Figure 270: Sales of leading drugs for Alzheimer's disease



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 271: Sales of leading drugs for Alzheimer's disease ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Aricept	Eisai/Pfizer	2,521	2,957	3,516	3,913	3,851	2,445
Namenda/Ebixa	Forest labs/Lundbeck	890	1,134	1,319	1,520	1,728	1,868
Exelon	Novartis	525	632	815	954	1,003	1,067
Razadyne/Reminyl	JnJ/Shire/Takeda	478	562	575	457	443	448

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Depression and affective disorders

- Global sales of drugs treating depression and affective disorders totalled $13bn in 2011.
- Sales growth has slowed due to patent expiration in class-leading products.
- Leading products include Cymbalta (Eli Lilly), Lexapro/Cipralex (Forest/Lundbeck), Paxil (GlaxoSmithKline) and Effexor (Pfizer).

Affective disorders are characterised by changes in mood (depression or mania). Depression is the more common state, ranging from mild to severe or psychotic depression. Symptoms of depression include emotional and biological components – emotional components encompassing symptoms such as misery, apathy, low motivation and low self-esteem, while the biological response includes a loss of appetite and sleep disturbance, among other symptoms. There are two types of depressive syndrome, namely, unipolar (75% of cases), in which mood swings are always in the same direction, and bipolar, in which depression alternates with mania (manic depression).

The World Health Organization estimates that depression affects up to 121 million globally, while US Surgeon General estimates prevalence at around 5-7% of the population. Depression is two to three times as frequent in females as in males and is most evident in adults between the ages of 25 and 44. An unfortunately common complication of depression is suicide, and a study by Mayo clinic estimates that about 2-9% of people with depression may attempt to commit suicide.

Physiology

As with most illnesses of the CNS, the physiological cause of affective disorders is unclear. The main theory of depression holds that it arises as a consequence of a functional deficit of neurotransmitters (such as serotonin and noradrenaline) at certain receptor sites in the brain. In contrast, mania is due to a functional excess at these same sites. In part, this theory is supported by the positive impact that drugs which increase the concentration of concentration of serotonin and noradrenaline at receptor sites have on depression.

Pharmacological treatment

The key neurotransmitters in depression and mania appear to be the monoamines, i.e. serotonin (5-HT) and noradrenaline. Consequently, the pharmacological approach to treat these symptoms has been to develop drugs which impact the level of these monoamines in particular regions of the brain. Several different classes of drugs have been developed over the years, including the tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin re-uptake inhibitors (SSRIs), and serotonin and norepinephrine re-uptake inhibitors (SNRIs). The latter two classes contain branded drugs which offer fewer side-effects, and hence account for the lion's share of today's depression market by sales. However, we expect sales of the branded drug segment will decline over the next few years with the expiry of patent protection for blockbusters such as Cipralex/Lexapro and Cymbalta in 2012 and 2013 respectively.

Tricyclic antidepressants (TCAs)

TCAs inhibit the uptake of noradrenaline and/or serotonin (5-HT) by monoaminergic nerve terminals, thus increasing their levels in the brain. However, most TCAs also have an impact on cholinergic receptors in the rest of the body, leading to troublesome anti-muscarinic side-effects such as dry mouth, blurred vision, constipation, sedation and urinary retention. They also have significant interactions with other drugs. Taken in overdose, they can be fatal, a potential disadvantage given their use by patients who may have suicidal tendencies.

Monoamine oxidase inhibitors (MAOIs)

MAOIs bind irreversibly to one or both forms of the cerebral enzyme, monoamine oxidase (MAO-A or B), inhibiting the breakdown of noradrenaline, dopamine and 5-HT, thus increasing their concentration at nerve terminals. MAO-A preferentially metabolizes 5-HT, noradrenaline, while both MAO-A and MAO-B break down dopamine. Hence, some of the newer MAOIs are selective inhibitors of MAO-A. MAOIs were among the first anti-depressant drugs to be developed. However, significant side-effects arose, in part because of the effect of these drugs on monoamine oxidase outside the central nervous system. Consequently, they have largely been displaced by the safer TCAs and SSRIs. As with TCAs, an overdose may be fatal.

Selective serotonin re-uptake inhibitors (SSRIs)

SSRIs show greater selectivity for 5-HT than TCAs and MAOIs. While their efficacy in treating the symptoms of depression is no greater than the TCAs, an improved side-effect profile helped them become the leading class of anti-depressants. As with other classes of anti-depressants, it typically requires 2-4 weeks before a therapeutic benefit may be seen. Common side-effects include nausea, insomnia, weight loss and loss of libido. However, their toxicity is less than that of the previous classes. Importantly, the efficacy and side-effect profile of the SSRIs has seen them used in a variety of other anxiety-related disorders, such as panic attacks, general anxiety disorder and obsessive-compulsive disorder. This increased usage has helped drive the overall size of the market for anti-depressants.

Serotonin and norepinephrine re-uptake inhibitors (SNRIs)

Like the SSRIs, the SNRIs offer similar efficacy in relieving depression symptoms while providing a more tolerable side effect profile compared with the TCAs. In particular, the SNRIs are often associated with a lower risk of decreased libido or weight gain. Some studies conducted comparing SSRIs and SNRIs suggest that SSRIs have been more effective in treating associated anxiety, while SNRIs have been more effective in treating severe depression.

Figure 272: Leading anti-depressants

Name	Generic	Class	Company	2011 sales
Cymbalta	duloxetine hydrochloride	SNRI	Eli Lilly	$4.2bn
Lexapro/Cipralex	escitalopram oxalate	SSRI	Forest Laboratories/Lundbeck	$3.3bn
Paxil	paroxetine hydrochloride	SSRI	GlaxoSmithKline	$0.7bn
Effexor	venlafaxine hydrochloride	SNRI	Pfizer	$0.7bn
Pristiq	desvenlafaxine succinate	SNRI	Pfizer	$0.6bn
Zoloft	sertraline hydrochloride	SSRI	Pfizer	$0.6bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Other indications

Outside affective disorders, anti-depressants have also found increasing use in anxiety-related indications. As mentioned, this broadening of the indication base has helped drive the growth of the entire class. Additional indications often include the following:

- **Panic disorder**: Panic disorder begins as a series of unexpected panic attacks, involving an intense terrifying fear similar to that caused by life-threatening danger. The attacks may be followed by over a month of persistent concern about having a further attack. Secondary to the panic attack, many patients subsequently develop agoraphobia (fear of public and open spaces).
- **Obsessive-compulsive disorder (OCD)**: OCD requires the presence of obsessions/compulsions that are severe enough to cause marked distress, to be time consuming, and to cause significant impairment in social or occupational functioning. Individuals often recognise that their obsessions (for example, cleanliness) or compulsions are excessive or unreasonable and attempt to ignore or suppress them. More than 50% of those suffering from OCD typically also suffer from another major psychiatric disorder.
- **Anxiety**: Historically, anxiety disorders have largely been treated with benzodiazepines, such as Valium. These act as GABA (gamma amino butyric acid) agonists, GABA having an inhibitory effect on the activity of certain CNS pathways and, consequently, producing a calming/sedating influence. However, several SSRIs have also demonstrated anxiolytic properties, particularly those which have the strongest effect on 5-HT. SSRIs are increasingly emerging as first-line therapy because of better tolerability and a lower risk of dependency. However, as they are mostly branded drugs at present, they are significantly more expensive than classical benzodiazepine therapy.
- **Social phobias**: The essential feature of social phobia is a marked and persistent fear of social or performance situations in which embarrassment may occur. Unlike other anxiety disorders, the reason for the fear is clearly identifiable, though the patient may not be able to control it.

Pipeline products

There remains high unmet need in depression, with patients often failing on the first prescribed drug. However, there is a general lack of new drugs with significantly different mechanisms of action. Pipeline products mainly focus on current known pathways but with altered receptor binding to provide an alternative product – such as similar efficacy but with lower side effects. One 'novel' drug is Lundbeck/Takeda's Lu AA21004 ('004), which is both a serotonin reuptake inhibitor and a stimulator of the serotonin receptor. While anti-depressive drugs are associated with a high incidence of side-effects as mentioned, '004 offers a potentially differentiated profile of good tolerability (primarily lower incidence of sexual dysfunction) and improved cognition. Followed mixed results in early Phase III studies, three recent Phase III trials have confirmed efficacy of '004 in depression and regulatory submission in both the US and Europe is planned for 2H12.

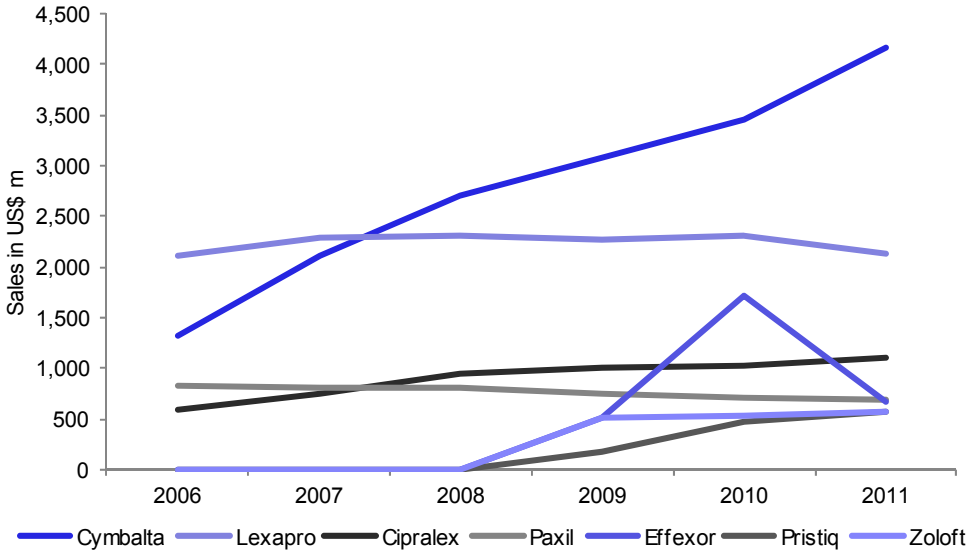
Figure 273: Selected late-stage drugs for depression

Name	Class	Company	Stage
Lu AA21004	Serotonin enhancer	Lundbeck/Takeda	Phase III
levomilnacipran	SNRI	Forest Laboratories/Pierre Fabre Medicament	Phase III
agomelatine	Melatonin MT1/MT2 agonist & 5-HT2C (serotonin) antagonist	Novartis/Servier	Phase III

Source: Company data

Sales

Figure 274: Sales of leading anti-depressants



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 275: Sales of leading anti-depressants ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Cymbalta	Eli Lilly	1,316	2,103	2,697	3,075	3,459	4,162
Lexapro	Forest Laboratories	2,106	2,292	2,301	2,270	2,300	2,138
Cipralex	Lundbeck	591	753	952	996	1,035	1,113
Paxil	GlaxoSmithKline	826	801	805	753	704	698
Effexor	Pfizer				520	1,718	678
Pristiq	Pfizer				181	466	577
Zoloft	Pfizer				516	532	573

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Attention deficit hyperactivity disorder (ADHD)

- Global sales of drugs treating ADHD totalled c.$4.8bn in 2011.
- Approximately 3-5% of school-aged children have been diagnosed with ADHD.
- The market is dominated by extended-release formulations of relatively old compounds.

Attention deficit hyperactivity disorder (ADHD) is the most common behavioural disorder among school-age children. It is estimated to affect 3-5% of children in the US, and is seen three to five times more often in boys than in girls. The condition is characterised by three key behaviours – inattentiveness, hyperactivity and impulsiveness – which diminish the patient's ability to function in normal areas of life. While traditionally considered a childhood disease, recent evidence suggests residual symptoms may persist into adulthood (indeed, adult ADHD has been a source of market growth in recent years). According to a NIMH funded study conducted by researchers from Harvard Medical School, an estimated 4.4% of adults in the US continue to experience symptoms and some disability related to ADHD.

ADHD is often difficult to diagnose and treat due to the lack of observable physiological signs, combined with a broad range of characteristic symptoms. Moreover, many ADHD-type behaviours may be linked to other causes, ranging from mild seizures to emotional disturbances. ADHD may also coexist with neurological conditions such as anxiety disorders or depression.

Given these complexities, this disorder was only officially recognised by the American Psychiatric Association in 1980, with specific diagnostic criteria in the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III). This was later updated in the latest edition of the manual, DSM-IV, recognizing three subtypes of ADHD – 1) Combined type, 2) Predominantly Inactive type and 3) Predominantly Hyperactive-Impulsive type. An ADHD diagnosis requires that children exhibit signs of inattention and/or hyperactivity and impulsivity that adversely affect their ability to function in at least two environments, such as school, home or social settings. The behaviour must appear before age 7, be excessive in comparison to that expected in children of the same age and must persist for at least six months. The full criteria are outlined on the next page.

While similar to the DSM-IV guidelines, the diagnostic criteria used in Europe are slightly narrower. Specifically, the European definition, which is based on the International Classifications of Diseases (ICD-10), requires that the child exhibit all three symptoms of inattention, hyperactivity and impulsivity. This stricter criteria, together with greater European scepticism regarding not just the validity of the disease but also its treatment with stimulant drugs, helps to explain the lower reported incidence of the condition in Europe.

Physiology

The cause of ADHD is unknown. The condition appears to run in families, with one in four affected children having a parent previously diagnosed with ADHD. In addition,

children whose mothers used alcohol, cigarettes or other drugs during pregnancy are at a heightened risk of developing ADHD. However, dietary factors – once thought to cause hyperactivity – have been proven to be uncorrelated.

Recent research has begun to suggest possible neurological abnormalities associated with ADHD. Imaging studies using PET (positron emission tomography) scans have indicated a possible dopamine deficit due to the increase in number of dopamine transporters. In addition, there appear to be malfunctions in certain parts of the brain, including areas responsible for concentration and the switching off of automatic responses.

Figure 276: Diagnostic criteria for ADHD

A) Either (1) or (2):
1) Six (or more) of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:
– Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
– Often has difficulty sustaining attention in tasks or play activities
– Often does not seem to listen when spoken to directly
– Often does not follow through on instructions and fails to finish schoolwork, chores or duties in the workplace (not due to oppositional behaviour or failure to understand instructions)
– Often has difficulty organising tasks and activities
– Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)
– Often loses things necessary for tasks or activities (e.g., toys, school assignments, pencils, books, or tools)
– Often is easily distracted by extraneous stimuli
– Often is forgetful in daily activities
2) Six (or more) of the following symptoms of hyperactivity-impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:
Hyperactivity
– Often fidgets with hands or feet or squirms in seat
– Often leaves seat in classroom or in other situations in which remaining seated is expected
– Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)
– Often has difficulty playing or engaging in leisure activities quietly
– Often is "on the go" or often acts as if "driven by a motor"
– Often talks excessively
Impulsivity
– Often blurts out answers before questions have been completed
– Often has difficulty awaiting turn
– Often interrupts or intrudes on others (e.g., butts into conversations or games)

B) Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7.

C) Some impairment from the symptoms is present in two or more settings (e.g., at school and at home).

D) There must be clear evidence of clinically significant impairment in social, academic or occupational functioning.

E) The symptoms do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia or other psychotic disorder and are not better accounted for by another mental disorder.

Source: Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)

Pharmacological treatment

Current clinical practice usually combines stimulant drugs with behavioural and cognitive therapies. Paradoxically, stimulants slow down a patient as they increase concentrations of dopamine, noradrenaline and adrenaline in parts of the brain that are thought to increase motivation and concentration in people with ADHD. Stimulant medication for ADHD can be broadly divided into methylphenidate and amphetamines. Different patients respond differently to each class, but overall efficacy appears broadly similar for methylphenidate and amphetamines (related to the recreational drug 'Speed'). Given the long-expired patent protection on the chemical compounds, most of the current branded products are primarily safer and longer-acting modifications of

traditional stimulants. This is perhaps a significant strategy in this class of drugs, because its users are primarily children, who would otherwise take the midday dose while at school.

Methyphenidates

Ritalin was the first drug used to treat ADHD, in the 1950s. It was dosed 2-3 times a day, which meant that children taking Ritalin needed to take the medication in school during lunch. Since then, different variations and formulations of methylphenidate have been launched which extend the duration of action greatly, increasing convenience and compliance. While Concerta currently leads this group, following several legal suits including to the Court of Appeals, Johnson & Johnson has entered into an agreement to supply and allow Watson Laboratories to market an authorized generic version of Concerta from May 2011. Actavis and Teva also launched generics in 2012.

Amphetamines

Amphetamine compounds were introduced for ADHD much later, with Adderall being the first amphetamine to receive approval in the US, in 1996. Since then, newer formulations have been developed which extend the duration of action to 12 hours or more (e.g. Adderall XR) and drug profiles, replicating the levels seen with medication taken two to three times a day.

Complicating treatment is the fact that both methylphenidate and amphetamines are Schedule II drugs in the US, meaning that they are government-controlled substances with specific regulations for distribution and dispensing. Although there is little risk of addiction, there is a potential for abuse at higher doses. Patients used to have to see their doctors to get their prescriptions refilled, but since 2007, they have been able to obtain up to 90 days of medication per visit. Shire's Vyvanse tries to address the issue of abuse, being formulated as an inactive prodrug which is later converted into an active form in the intestinal tract/liver. It does not produce the stimulant effect if taken by other methods, e.g. intravenously. However, it is still classified as a Schedule II drug.

Non-stimulants

Lilly's Strattera was the first non-stimulant drug to be developed. After an initial rapid uptake, Stattera's market share plateaued, largely due to a slower onset of action and more modest efficacy relative to the stimulants. In addition, in 2004, the FDA added a warning to Strattera's label regarding a risk of liver toxicity, and in 2005, the FDA ordered a black box warning be included on the increased risk of suicidal thinking. Prescriptions of the drug have declined as a result. Shire's Intuniv, a once-daily alpha-2A adrenergic receptor agonist, was approved by the FDA in September 2009 and is currently the only alternative to Strattera in the non-stimulants category. It is thought to act on the prefrontal cortex to improve concentration and memory, and is targeted at managing disruptive behaviour (e.g. inattention, hyperactivity, aggression). Additionally, as it is not a stimulant, it is therefore not a scheduled drug, allowing Shire provide samples of the product to physicians.

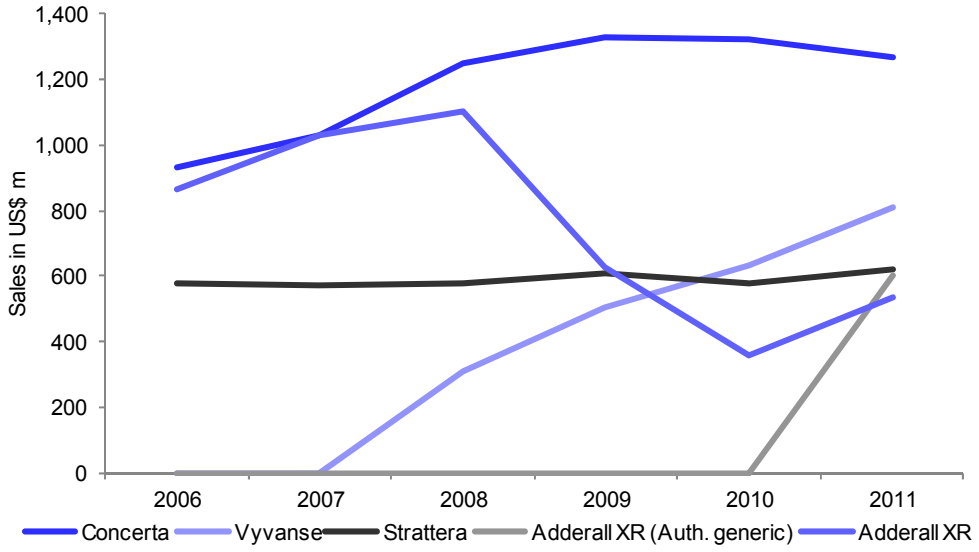
Clinical end-points

Clinical trial requirements are not as well established for ADHD as for other indications, given the historical lack of understanding and definition of the condition. This is evidenced by the variety of diagnostic rating scales used in clinical trials. Among these are the Conner's Inattention/Overactivity with Aggression Scale (IOWA), the Conner's Global Index Scale (TCGIS) and the ADHD Rating Scale-IV (ADHD-RS). In fact, Lilly developed its own parent-rated diary to help measure the efficacy of Strattera.

Pipeline products

Shire remains the most active company in this area, and is currently assessing a pro-drug formulation of Intuniv which uses the same technology (CarrierWave) as Vyvanse. There appear to be no major advances in treatment in current pipelines.

Figure 277: Sales of leading ADHD drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 278: Sales of leading ADHD drugs ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Concerta	Johnson & Johnson	930	1,028	1,247	1,326	1,319	1,268
Vyvanse	Shire		-	309	505	634	809
Strattera	Eli Lilly	579	569	580	609	577	620
Adderall XR (Auth. generic)	Watson Pharmaceuticals		-	-	-	-	601
Adderall XR	Shire	864	1,031	1,102	627	361	533

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Multiple sclerosis

- Worldwide sales of multiple sclerosis drugs totalled c.$12.5bn in 2011, with a CAGR of c.17% from 2006-11.
- Multiple sclerosis affects approximately 350,000 people in the US and 2.5 million globally.
- The market is dominated by interferons, including Biogen IDEC's Avonex, Merck KGaA's Rebif and Bayer's Betaseron. However, new oral therapies are set to revolutionise treatment.

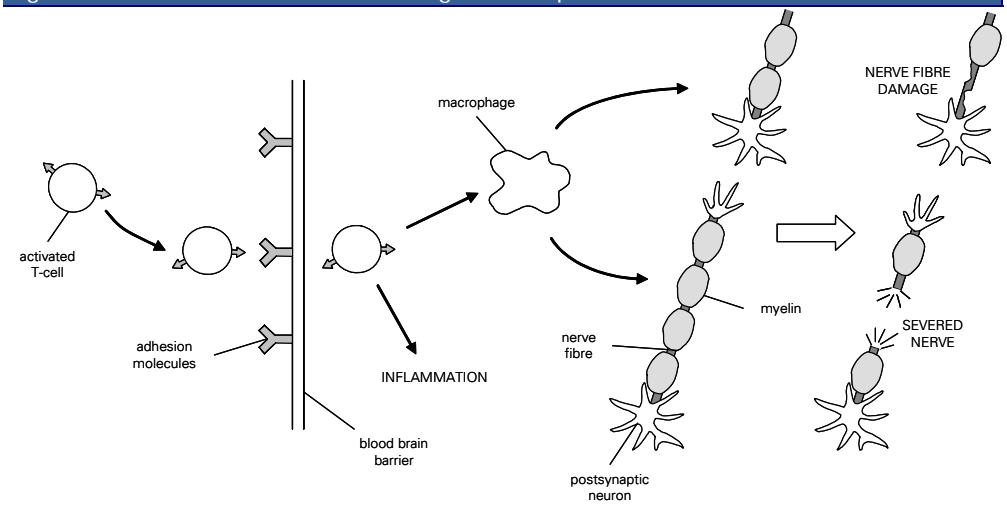
Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS), most commonly diagnosed in adults between the ages of 25 and 40 and twice as common in women as in men. While the exact cause of MS remains a mystery, epidemiology studies imply both a genetic and an environmental component to the disease.

Physiology

MS is characterised by inflammation occurring in the brain and the spinal cord, resulting in a loss of the myelin sheath which encapsulates nerve fibres. In addition to its protective role, myelin facilitates the smooth, high-speed transmission of chemical messages between the brain, spinal cord and the rest of the body. MS is thought to arise as a result of a cellular immune response against oligodendrocytes, which nourish and replenish the myelin sheaths in the CNS. Consequently, there is a steady loss of myelin sheaths in the CNS, leading to an impaired transmission of neural impulses.

On a cellular level, several malfunctions in the immune system occur (Figure 279). First, certain immune system cells, known as T-cells, become activated and primed to attack the body's own myelin tissues. Next, the blood-brain barrier, which usually prevents large molecules from passing from the bloodstream into the CNS, becomes permeable to the activated T-cells. This occurs due to the overexpression of so-called 'adhesion molecules' that line the blood vessels and facilitate the movement of these cells across the blood-brain barrier. Once inside the CNS, the activated T-cells recruit macrophages and initiate an inflammatory response.

Figure 279: Mechanism of nerve damage in multiple sclerosis



Source: Deutsche Bank

The progressive symptoms of MS typically include blurred vision, muscle weakness and lack of coordination. Some patients also experience cognitive impairment such as difficulty with concentration, memory or judgment. Based on the frequency and resolution of these symptoms, MS patients are classified into four primary categories listed below.

Figure 280: Classification of multiple sclerosis

Type	Incidence	Characteristics
Relapsing-remitting (RRMS)	40%	Abrupt onset of periods of attacks, followed by partial or total remission
Secondary progressive (SPMS)	40%	Initial RRMS, followed by steady progression with few flares
Primary progressive (PPMS)	10%	Rapid deterioration from onset, with only brief periods of remission or stabilization
Progressive-Relapsing (PRMS)	10%	Gradual progression of symptoms with periods of symptomatic relapses

Source: F. D. Lublin et al, Defining the Clinical Course of Multiple Sclerosis: Results of an International Survey (Neurology 46:907-911, 1996)

Pharmacological treatment

As no known cure for MS exists, treatment focuses on drugs designed to reduce the severity and frequency of attacks. Acute exacerbations are usually treated with short-term, powerful steroids or muscle relaxants, whereas prevention of relapses and progressive nerve damage has traditionally relied on disease-modifying drugs, the most commonly prescribed of which are interferons. The exact mechanism by which the interferons slow disease progression is unknown, but there is evidence suggesting they may down-regulate certain inflammatory cytokines, inhibit T-cell proliferation and/or reduce blood-brain barrier permeability and T-cell migration into the CNS.

Interferons/ Copaxone

There are currently three interferons on the market: Avonex (interferon β-1a), Rebif (interferon β-1a) and Betaseron/ Extavia (interferon β-1b). A fourth non-interferon agent, Copaxone, has also been available for some time and has slowly made its way into usage as both a first line agent and one for patients who fail interferon therapy. Copaxone is a polymer composed of four amino acids found in the myelin sheath. Its

mechanism of action is not clear, but it is believed to activate cells which suppress the immune response against myelin.

Integrin receptor antagonist MAb

In late 2004, the FDA approved Elan/Biogen IDEC's Tysabri (natalizumab), a novel monoclonal antibody which is the first in an entirely new class of drug to treat MS. Tysabri binds to α4 integrin, a receptor present on T-cells that facilitates migration across the blood-brain barrier and thereby inhibits T-cell trafficking into the CNS and destruction of myelin tissue. Based on clinical data, which suggested a significant improvement over the interferons, the FDA allowed an accelerated regulatory filing and approved the drug in November 2004. However, less than four months after launch, Tysabri suffered a major setback when three patients were diagnosed with a rare and frequently fatal condition known as progressive multifocal leukoencephalopathy (PML). This led Elan and Biogen to withdraw the drug from the market. The FDA allowed Tysabri to be marketed again in 2006 with a special prescribing program, though PML cases continued to be reported. The increased risk for developing PML was later linked to positive assays for JC virus antibodies and a test was developed to determine antibody status before prescribing Tysabri. The FDA updated the label in January 2012 to include information about the JCV assay. This has inspired more confidence in physicians and patients, and sales have continued to increase rapidly despite the risk.

Sphingosine 1-phosphate receptor modulator

Novartis' Gilenya (fingolimod) was the first oral disease-modifying MS treatment to be approved by the FDA in 2010, for relapsing forms of the disease. It sequesters immune cells in the lymph nodes, preventing them from entering the CNS, while still allowing them to respond to infections which filter through the lymphatic system. Late stage studies showed significantly lower relapse rates (c. half) vis-à-vis interferon β-1a, with fewer new and enlarging lesions. There were some concerns over safety when a patient died after the first dose of Gilenya, but a reevaluation of clinical and post-market data by the FDA could not conclude that the incident was linked to the drug. However, the agency expressed concerns over cardiovascular side effects and recommended extended cardiovascular monitoring for patients starting Gilenya while adding a contraindication for those with certain pre-existing or recent heart conditions or stroke.

Potassium channel blocker

Acorda/Biogen Idec's Ampyra/ Fampyra (fampridine), was approved by the FDA to improve walking speed in patients with multiple sclerosis. It is a potassium channel blocker and acts by enhancing the action potential and improving firing in poor-conducting myelin depleted nerves. Famipridine has been found to work best in chronic progressive MS and improves symptoms (though not the progression of the disease). The drug can cause seizures if the recommended dose is exceeded, and is contraindicated in those with seizure history or with impaired renal function.

Figure 281: Comparison of leading disease-modifying multiple sclerosis drugs

	Avonex	Rebif	Betaseron	Tysabri	Gilenya
Generic	interferon b-1a	interferon b-1a	interferon b-1b	natalizumab	fingolimod
Company	Biogen	Merck KGaA/Pfizer	Bayer	Elan/Biogen Idec	Novartis
Launch (USA/Europe)	1996/1997	2002/1998	1993/1996	2004	2010/2011
Approved indications	RRMS	RRMS	RRMS, PPMS (Europe only)	RRMS	RRMS, PRMS
Route of delivery	intramuscular	Subcutaneous	subcutaneous	intravenous	oral
Dose	30 mg	22 or 44 mg	250 mg	300mg	0.5 mg
Dosing frequency	1x/week	3x/week	3x/week	1x/4 weeks	1x/day
Annual relapse rate reduction vs. placebo	-18%	-30%	-31%	-67%	-55%
% patients exacerbation free (placebo) at two yrs	38% (26%)	32% (15%)	25% (16%)	67% (41%)	70% (46%)

Source: Deutsche Bank, company data

Clinical end-points

The severity of MS-induced disability is most often evaluated via the Expanded Disability Status Scale (EDSS), a 10-point scale divided into half-point increments. Unfortunately, this scale (and many of its variants) has received much criticism due to its high subjectivity, non-linearity and low test-retest reliability. Given these deficiencies, most investigators employ more objective measures as primary end-points, including relapse rates and the number of MS lesions visible via magnetic resonance imaging (MRI) scans.

It is also worth noting that with substantial evidence supporting the long-term efficacy of the interferon drugs, clinical evaluation may begin to rely on head-to-head studies vs. interferon therapy rather than traditional placebo-controlled trials.

Pipeline products

MS has traditionally been a very risky area for product development, with a number of drug candidates having failed in late-stage trials. One example is Merck KGaA's oral MS drug, cladribine, where clinical development was terminated due to safety concerns.

The focus of the MS pipeline is now on the development of an orally delivered (versus injectable) product. Biogen Idec recently submitted BG-12, its twice-daily oral MS drug, to US and EU authorities for approval. BG-12 (dimethyl fumarate) has a protective influence on cells by activating the detoxifying Nrf2 pathway. This in turn releases an array of enzymes that repair damaged proteins and decrease inflammation and tissue damage, thereby preventing myelin loss. Positive results from the phase III DEFINE study reported much lower relapse rates than placebo.

Sanofi has also submitted for approval its oral once-daily drug, Aubagio (teriflunomide), which it obtained as part of its Genzyme acquisition. Aubagio is a selective inhibitor of pyrimidine synthesis and blocks the proliferation of T-cells and B-cells, reducing the inflammation process. Relapse rates observed with Aubagio were similar to those with interferons, but higher than with Gilenya or Tysabri, while disability progression rates were comparable with Gilenya. When administered together with interferon therapy, it demonstrated the ability to reduce the number of brain lesions beyond that achieved by interferon therapy alone. Aubagio is being evaluated as adjunct therapy to interferon β.

Sanofi/ Bayer's Lemtrada (alemtuzumab) is one-cycle a year injectable for relapsing forms of multiple sclerosis. Lemtrada targets the B and T lymphocytes that express CD52 and clears them from the bloodstream. These cells repopulate over a variable period of time before the next dose is administered a year later. The antibody-producing capacity is not affected, thus the immunosuppressive effect is minimal. It is hypothesized that the repopulated lymphocytes secrete neurotrophins which may enhance survival and function of neurons. Phase III studies compared Lemtrada to Rebif, and demonstrated significant advantage with lower relapse rates, slower disability progression and indeed, reversing of disability in some patients.

Teva Pharmaceuticals and Active Biotech are working on an oral phase III drug, laquinimod, which reduces immune cell infiltration of the CNS. By preventing T cells from crossing the blood brain barrier, it exerts a protective effect and may also increase the levels of protective proteins. Phase III studies showed significant reduction in relapse rate and disability progression vs placebo. However, following talks with the FDA, Teva decided to plan further phase III studies and delay filing an NDA.

Biogen is investigating PEGylated interferon β-1a, which has been granted fast track designation by the FDA. This modified version of the interferon may increase half-life and efficacy versus the available drug. Early stage results were positive. Several other products for MS are in late stage development, most targeted at specific components of inflammation. Roche/ Biogen are developing ocrelizumab, an anti-CD20 drug now in phase III trials. Biogen in collaboration with Abbott is also developing Zenapax (daclizumab), an anti-IL2 antibody that decreases CD25 expression. The drug met its primary and secondary end-points in preliminary results from phase II trials.

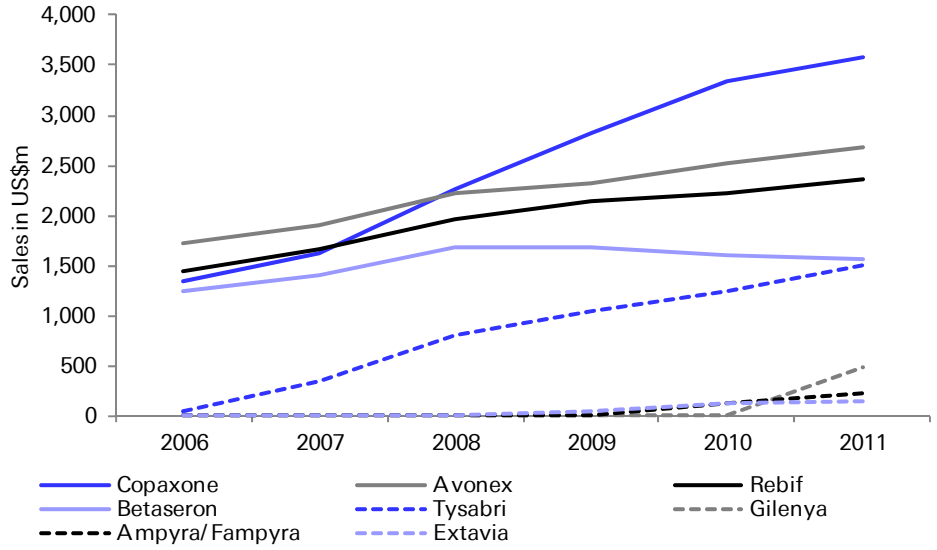
Figure 282: Selected late-stage pipeline products for multiple sclerosis

Name	Generic	Company	Stage
BG-12	BG-12	Biogen Idec	Filed
Aubagio	teriflunomide	Sanofi	Filed
Lemtrada	alemtuzumab	Sanofi/ Bayer	Filed
Laquinimod	Laquinimod	Teva	Phase III
PEGylated-IFN β-1a	PEGylated-IFN β-1a	Biogen Idec	Phase III
RG1594	Ocrelizumab	Roche/ Biogen	Phase III
Zenapax	Daclizumab	Biogen/ Abbott	Phase III
Ponesimod	Ponesimod	Actelion	Phase II
Arzerra	Ofatumumab	GlaxoSmithKline	Phase II
BAF312	BAF312	Novartis	Phase II

Source: Company data, Deutsche Bank

Sales

Figure 283: Sales of leading multiple sclerosis drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 284: Sales of leading multiple sclerosis drugs ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Copaxone	Teva/ Sanofi	1,343	1,614	2,262	2,826	3,341	3,580
Avonex	Biogen Idec	1,725	1,895	2,217	2,323	2,518	2,687
Rebif	Merck KGaA	1,452	1,670	1,956	2,142	2,214	2,354
Betaseron	Bayer	1,245	1,410	1,681	1,692	1,600	1,555
Tysabri	Biogen/ Elan	38	343	814	1,053	1,241	1,500
Gilenya	Novartis					15	494
Ampyra/ Fampyra	Biogen/ Acorda					133	224
Extavia	Novartis				49	124	154

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Epilepsy

- Global sales of anti-epileptic drugs totaled $5.8bn in 2011.
- Nearly 50 million people worldwide suffer from epilepsy, 90% of them in developing countries.
- Leading products include Keppra (UCB), Lamictal (GlaxoSmithkline) and Depakine (Sanofi).

Epilepsy is a chronic neurological condition characterized by recurrent seizures (also known as convulsions or 'fits'). This is due to changes in certain parts of the brain which causes it to be easily excitable and prone to sending abnormal electrical impulses, leading to uncontrollable jerking motions or even loss of muscle tone and/or awareness for others. While an estimated one in ten people may experience a seizure at some time, the diagnosis of epilepsy requires the occurrence of two or more seizures. There are c.2 million people in the US and c.50 million people in the world with epilepsy. It is most common in children and in the elderly, due to the risk factors in these age groups. There is no cure for epilepsy although most children with the condition tend to experience fewer seizures as they get older. Anti-epileptic drugs reduce the occurrence of seizures but about one-third of patients continue to experience seizures despite treatment.

Seizure may be classified as generalized or focal (also known as partial). Generalized seizures involve abnormal electrical activity in the whole brain, typically leading to a loss of consciousness and changes in muscle tone affecting the whole body (e.g. tonic-clonic or atonic seizures). This is typically followed by a period of drowsiness, which may last an hour or longer, and a loss of memory around the events leading to the seizure. Focal seizures start in part of the brain, with the patient typically still conscious initially while experiencing symptoms such as uncontrolled movements localized to a part of the body. These episodes typically last for several minutes. Occasionally, what starts as a focal seizure may progress to become a generalized seizure.

Physiology

Epilepsy may be due to a medical condition or injury affecting the brain, e.g. stroke, infection, brain tumour, which alters the electrical activity of the surrounding tissue, resulting in the onset of abnormal electrical impulses which travel through the brain. However, in many instances, no specific cause is found.

Pharmacological treatment

Patients with infrequent seizures typically do not require medication and are counseled regarding what to expect and the appropriate response should a seizure recur. Patients who experience frequent seizures are started on anti-epileptic medication and c.70% of patients are able to live symptom free through the use of medication.

Anti-epileptic drugs (AEDs) may be divided into several categories, depending on their primary mode of action (although most act via several mechanisms).

Sodium channel blockers

Following an electrical impulse, the sodium channels are typically inactive for a short period of time, where any subsequent impulses are no longer conducted. This is also

known as the refractory period. Sodium channel blockers stabilize these sodium channels in their inactive form, and hence block the subsequent spread of abnormal impulses. Phenytoin and carbamazepine belong to this class and have been used in the treatment of partial and generalized seizures since 1938 and 1968, respectively. Variants of these drugs were later developed e.g. fosphenytoin (Cerebyx) and oxcarbazepine (Trileptal), which offered similar efficacy with potentially fewer side effects. Newer drugs in this class include Lamotrigine (Lamictal), which also inhibits the release of glutamate, and Lacosamide (Vimpat), which is thought to enhance the slow inactivation of sodium channels (thereby stabilizing the brain).

GABA receptor agonist

GABA (or Gamma-AminoButyric Acid) is an important inhibitory neurotransmitter in the brain. It acts primarily by increasing the negative charge inside nerves (a state known of hyperpolarization), making it more difficult for an electrical impulse to be transmitted. Drugs in this class bind to GABA receptors to exert their effect, and include benzodiazepines (e.g. lorazepam, diazepam, clonazepam) and barbituates (e.g. phenobarbital, primidone).

GABA reuptake inhibitors

The action of GABA at the synaptic cleft may be terminated by reuptake into nerves, where it is metabolized. GABA reuptake inhibitors block the reuptake of GABA by inhibiting the GABA transporter, thus prolonging its inhibitory activity. The principal drug in this class is tiagabine (Gabitril), which is approved for use as an adjunct in partial epilepsy in patients that are refractory to treatment.

GABA transaminase inhibitors

GABA is also metabolized by transamination in the synaptic cleft and hence inhibition of this process results in an increased concentration of GABA. The main drug in this class is vigabatrin (Sabril) which binds irreversibly to GABA transaminase to increase the extracellular concentration of GABA in the brain. However, while highly effective, its use has been limited by its side effects, which include a gradual (occasionally permanent) loss of peripheral vision. As a result of this, it is only approved in the US for the treatment of infantile spasms (West Syndrome) and for adults with refractory complex partial seizures. However, prescription in both indications requires extensive risk mitigation plans.

Glutamic Acid Decarboxylase enhancer

GABA is produced from glutamic acid by the enzyme glutamic acid decarboxylase. Several drugs such as sodium valproate, divalproex sodium (Depakote) and gabapentin (neurontin) are postulated to act on this enzyme, thereby enhancing the production of GABA. In addition to this, valproate is also a sodium channel blocker while gabapentin is also an inhibitor of GABA transaminase.

Glutamate blockers

As mentioned, glutamate is an important excitatory neurotransmitter in the brain and there are several receptor subtypes (e.g. AMPA, NMDA) which are involved in various neurological functions. An example of this class is topiramate (Topamax), which in addition to being a AMPA subtype glutamate inhibitor, is also a sodium channel inhibitor and a GABA enhancer.

Potassium channel opener

Potassium is an electrolyte which plays an important role in the generation and transmission of electrical impulses in the brain. Ezogabine (Potiga) is a newly approved drug which acts as a potassium channel opener. This is thought to lead to

hyperpolarisation and a reduction in brain excitability. Ezogabine has a side effect of urinary retention, which required a Risk Evaluation and Mitigation Strategy (REMS) from GSK.

Other anti-epileptics

Levetiracetam (Keppra) is a potent anti-epileptic drug for which the mechanism of action is not clearly understood. It does not bind to traditional receptors such as GABA, glutamate or sodium channels as previously understood. Instead, it has been found to bind to a site in rat brain tissue called synaptic vesicle protein SV2A, the significance of which is not well understood. However, its novel mechanism of action, relatively clean side effect profile and lack of interactions with other drugs makes it a preferred candidate adjunct treatment for patients who continue to experience break-through seizures while on medication.

Figure 285: Leading anti-epileptic drugs

Name	Generic	Class	Company	2011 sales
Keppra	levetiracetam	SV2A	UCB	$1.3bn
Lamictal	lamotrigine	Sodium channel blocker	GlaxoSmithKline	$0.9bn
Depakine	valproate sodium	GABA receptor agonist	Sanofi	$0.5bn
Topamax	topiramate	Glutamate blocker	Johnson & Johnson	$0.5bn
Tegretol	carbamazepine	Sodium channel blocker	Novartis	$0.4bn
Vimpat	lacosamide	CRMP-2 modulator	UCB	$0.3bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Clinical end-points

Common clinical endpoints include a demonstration of a decrease in frequency of seizures measured over a time period (e.g. 28 day seizure frequency, mean weekly frequency). Other measures of interest include the percentage of patients who were seizure free while on treatment. Epilepsy drugs are frequently associated with side effects and drug interactions with other epilepsy drugs. Given that most patients tend to be on more than one AED, the clinical profile of any new drug is therefore an important consideration in determining how it fits into the current treatment paradigm.

Pipeline products

The majority of the epilepsy market is dominated by cheap generics. It is therefore important for any new developmental candidate to differentiate itself, either through a novel mechanism of action, an improved efficacy or a more convenient formulation. As with any chronic disease, penetration will initially be difficult as patients who are stable on chronic therapy are loathe to change their medication, thereby restricting initial market share gains to newly diagnosed patients. However, once established, this then works in the incumbent's favour, as evidenced by the comparative slower rate of generic erosion in this market.

One prospective compound with a novel mechanism of action is Eisai's Fycompa (perampanel), a highly selective non-competitive AMPA antagonist. Thus far the data has been encouraging, with positive data from three pivotal Phase III studies establishing Fycompa's efficacy as an adjunctive treatment in partial seizures. Eisai received a positive CHMP opinion for the use of Fycompa (Perampanel) as an adjunctive treatment of partial-onset seizures and has PDUFA action date of 22 Oct 2012 in the US.

As an example of an incremental improvement, Dainippon Sumitomo's subsidiary, Sunovion, is developing eslicarbazepine (Stedesa), a next generation carbamazepine. Also known as Zebinix, it has received European regulatory approval where it is marketed by Eisai. However, Sunovion received a Complete Response letter from the FDA in May 2010, which resulted in Sunovion having to conduct an additional Phase III study. The company guides that it expects to resubmit its application, together with results from the latest trial, in 3Q 2012.

UCB is developing Brivaracetam, a next generation follow-on to levetiracetam (Keppra). Brivaracetam has a similar mode of action in binding to synaptic vesicle protein 2A and has an additional inhibitory activity on sodium channels. Clinical data has been mixed with Brivaracetam meeting its primary endpoint in one of the two phase III studies. UCB is conducting a third confirmatory study and results are expected in 1H 2013.

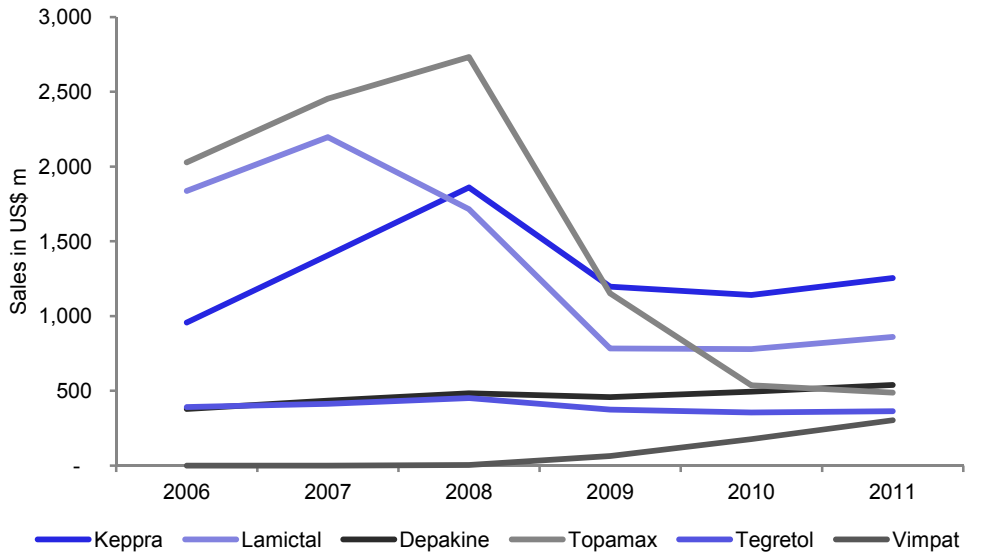
Figure 286: Selected late-stage drugs for epilepsy

Name	Class	Company	Stage
Fycompa (perampanel)	AMPA antagonist	Eisai	Filed
Zebenix/Stedesa (eslicarbazepine)	Sodium channel blocker	Sunovion/Eisai/BIAL	Marketed/Phase III
Brivaracetam	SV2A	UCB	III

Source: Company data

Sales

Figure 287: Sales of leading drugs for epilepsy



Source: Company data, EvaluatePharma, Deutsche Bank estimates

Figure 288: Sales of leading drugs for epilepsy ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Keppra	UCB	956	1,407	1,860	1,196	1,140	1,254
Lamictal	GlaxoSmithKline	1,836	2,196	1,714	783	779	860
Depakine	Sanofi	378	433	483	459	494	540
Topamax	Johnson & Johnson	2,027	2,453	2,731	1,151	538	488
Tegretol	Novartis	391	413	451	375	355	364
Vimpat	UCB	-	-	3	64	176	303

Source: Company data, EvaluatePharma, Deutsche Bank estimates

Migraine

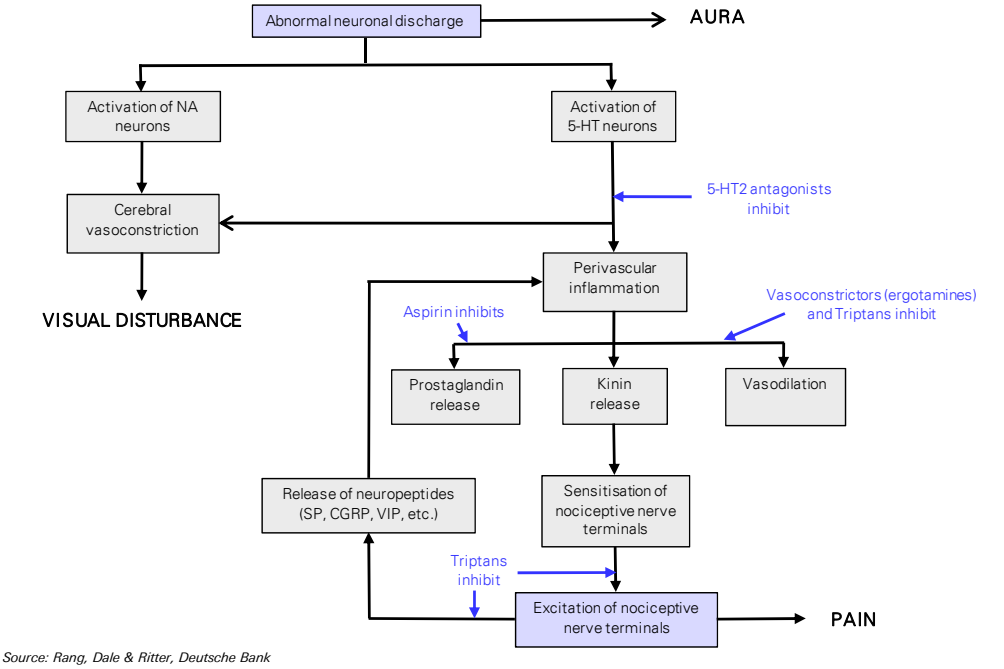
- Global sales of drugs treating migraine totalled c.$2.6bn in 2011.
- Leading products are triptans; such as Maxalt (Merck), Zomig (AstraZeneca), Relpax (Pfizer) and Imitrex (GlaxoSmithKline).

Migraine is a common condition affecting 10-15% of the population. Sufferers experience blinding headaches and nausea which can last several hours. According to the classical definition of migraine, patients typically experience visual disturbances (aura), e.g. white flashing lights or distorted view of objects, prior to the onset of the headaches. When present, these disturbances help physicians to diagnose the condition and prescribe the necessary medication. However, the majority of migraine sufferers (approximately 85%) do not experience an initial aura. Consequently, they are harder for physicians to diagnose and many patients as a result do not receive the appropriate medication.

Physiology

Migraine can be triggered by a number of stimuli, e.g. diet, menstruation, stress and medications. Unfortunately, the exact mechanism by which migraine occurs remains unknown, though a number of hypotheses have been put forward. One theory holds that migraine may originate as a result of an abnormal neuronal discharge, followed by spasm and dilation of the blood vessels in the brain. This is illustrated in Figure 289.

Figure 289: Theory of migraine



Source: Rang, Dale & Ritter, Deutsche Bank

This theory suggests that precipitating stimuli causes the neuronal discharge to occur, which triggers the hyperactivity of nerve cells in a certain area of the brain, and the release of large amounts of neuropeptides, e.g. noradrenalin and serotonin (5-HT). These neuropeptides stimulate the blood vessels to the visual centres in the brain to

narrow (cerebral vasoconstriction), resulting in the characteristic visual disturbances/aura experienced by the patient. The subsequent dilation of the blood vessels and associated inflammation is thought to be the source of the headaches which follow in migraine.

Pharmacological treatment

A range of treatments is available for migraine, depending on the severity of the condition.

- **Mild to moderate cases** are treated using over-the-counter medicines such as:
  - **Simple analgesics**, including paracetamol, which restricts the production of prostaglandins, thereby reducing but not completely eradicating the pain experienced; and
  - **Non-steroidal anti-inflammatory drugs, (NSAIDs)** such as aspirin and ibuprofen, which reduce the level of inflammation seen outside the brain and subsequently, vasodilation and pain.
- **Moderate to severe cases** are treated with prescription medicines that include:
  - older **ergotamines** (vasoconstrictors), which as 5-HT1 antagonists inhibit the presynaptic activities that lead to pain; and
  - newer **triptans**, such as GlaxoSmithKline's Imitrex (sumatriptan), which specifically target the 5-HT1D receptors believed to be responsible for vasodilation and pain. The drugs initiate vasoconstriction and thus bring about pain relief. This group of drugs now accounts for over 90% of retail migraine prescriptions in the US.

Imitrex was the first triptan on the market. Launched in 1993, it used to command more than 50% market share due to its high efficacy. Other triptans were subsequently launched between 1997 and 2003, but these have only led to modest market expansion. When sumatriptan went off-patent in 2009, the market size by value shrank as generic competition increased.

Surveys conducted in the US showed that only 1 in 10 patients receives appropriate treatment, and that more than 50% of patients with migraine are undiagnosed. One reason for this is that the vast majority of patients without the classical symptoms of aura may be incorrectly diagnosed. Consequently, there remains significant market potential in this indication.

Figure 290: Leading drugs for migraine

Name	Generic	Company	2011sales ($)
Maxalt	rizatriptan benzoate	Merck & Co	$0.6bn
Zomig	zolmitriptan	AstraZeneca	$0.4bn
Relpax	eletriptan hydrobromide	Pfizer	$0.3bn
Imitrex	sumatriptan succinate	GlaxoSmithKline	$0.3bn
Axert	almotriptan malate	Johnson & Johnson	$0.2bn
Amerge	naratriptan hydrochloride	GlaxoSmithKline	$0.1bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Clinical end-points

Clinical end-points are defined as the relief of moderate or severe pain to no or mild pain without the use of additional medication after a set time period (typically two or four hours).

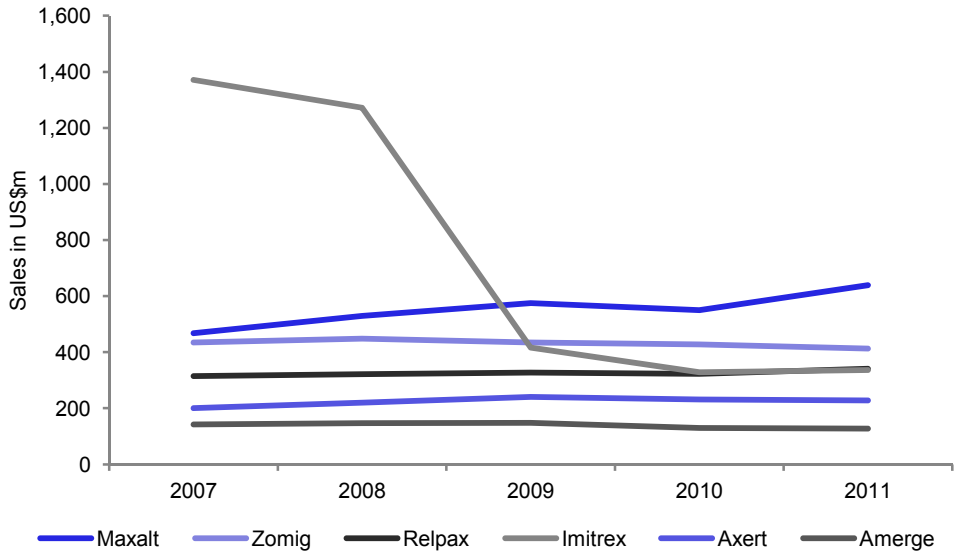
Pipeline products

Given the decline of the category following the loss of patent protection of leading products, together with the strong efficacy and safety profile of the triptans, there is little of note in the pipeline. MAP Pharmaceuticals' Levadex, which is an orally inhaled novel formulation of the intravenous anti-migraine drug dihydroergotamine, received a complete response letter from the FDA in March 2012, raising issues related to chemistry, manufacturing and controls (CMC). Importantly, no issues were raised with regard to efficacy or safety. MAP Pharma is working to address the issues raised and there are hopes that the drug may yet make it to the market.

Nupathe is developing the first transdermal patch for the treatment of migraine. NP101 aims to deliver sumatriptan across the skin, which theoretically offers a faster onset of pain relief. According to the company, the patch controls the delivery of sumatriptan, which regulates the plasma levels of the drug and is associated with a lower incidence of side-effects. Nupathe received a complete response letter in August 2011 citing questions relating to CMC issues. The company has addressed these questions and has resubmitted its application.

Sales

Figure 291: Sales of leading drugs for migraine



Source: Company data, EvaluatePharma, Deutsche Bank estimates

Figure 292: Sales of leading drugs for migraine ($ m)

Name	Company	2007	2008	2009	2010	2011
Maxalt	Merck & Co	467	529	575	550	639
Zomig	AstraZeneca	434	448	434	428	413
Relpax	Pfizer	315	321	327	323	341
Imitrex	GlaxoSmithKline	1,371	1,272	416	328	337
Axert	Johnson & Johnson	200	220	240	231	228
Amerge	GlaxoSmithKline	142	146	148	129	128

Source: Company data, EvaluatePharma, Deutsche Bank estimates

Introduction to oncology

- Global sales of oncology drugs totalled c.$62bn in 2011.
- Sales growth of upwards of 10% p.a. has been driven by an ageing population and novel agents, but the outlook for future growth has been modestly tempered by the arrival of generic chemotherapies and potentially biosimilars in the future.
- Leading companies include Roche and Novartis.

Introduction

Cancer is one of the major causes of death in the developed world. Roughly one in four people will die from some form of cancer, while almost one in two will suffer from a cancer at some point in their lives. To an extent the disease is a function of ageing and, as such, it is largely prevalent in older age groups, with incidence rising as a result of demographic changes in the developed world. There are many types of cancer. However, there is still no known cure for later-stage diseases, though some types of cancer may be controlled with medication.

Cancer (also called a tumour or neoplasm) is a disease in which the body's cells divide and multiply in an uncontrolled manner. Cancer is usually thought of as benign or malignant. Malignant cancer are usually invasive and when discovered, the cancer cells may have encroached into to the surrounding tissues. In addition, when malignant cancers spread to other parts of the body (via the blood or lymphatic system), these are then termed metastatic. For example, in metastatic breast cancer, breast cells that would normally be unable to develop outside the breasts would have spread to other organs such as the bone, lung, liver or brain. This makes the disease harder to treat and is associated with a poor five-year survival. By contrast, if a tumour is benign, it has uncontrolled growth but does not have the potential to invade surrounding tissue or metastasize.

The biology of cancer

The normal division and multiplication of human cells is controlled by several factors. The body releases various growth messengers called cyclins and cyclin-dependent enzymes which bind to cell receptors and stimulate a cell to start dividing. Genes called proto-oncogenes, located on human DNA (for example, the ras gene), control the production of these messengers and the production of their cell receptors and signal transducers. In turn, these growth-initiating messengers are regulated by several negative feedback mechanisms. Proteins which bind to the growth messengers and inhibit their action are also encoded by various genes, in particular, tumour suppressor genes such as the p53 gene and the Rb gene. In effect, these genes act as brakes on the replication system.

Once cell division is initiated, the cell's DNA is replicated and the proteins required to create a new cell are produced. Importantly, the process of DNA replication includes checks designed to ensure accuracy. An example of this is the p53 gene, which encourages cell self-destruction (apoptosis) if the DNA is damaged.

Cancer is generally a multi-stage process, the accumulation of several mutations in the cell's DNA which collectively bypass a cell's normal checks and balances. These

mutations may be inherited or may be caused by exposure to a DNA-corrupting substance (i.e. carcinogens such as radiation) or viral damage, for example. However, the result is normally one of the following:

- Tumour-suppressor genes are inactivated. Mutations in p53 are the most common mutations found in human cancer cells.
- Proto-oncogenes become overactive and become oncogenes, promoting uncontrollable cell division (in 20-30% of cancers, the ras gene has mutated).

Staging of cancer

The treatment options available to a patient usually depend on the type of cancer and the spread of cancer cells, i.e. the stage of the disease. This is broadly divided into local, regional and metastatic disease. A summary of cancer types, including incidence and survival rates, can be found in Figure 293.

Figure 293: Incidence, death and survival rates for key cancer types in the US

			---------- 5-year survival ----------			
Cancer type	**New cases**	**Deaths**	**Overall**	**Local**	**Regional**	**Distant**
Lung	221,130	156,940	15%	50%	21%	3%
Breast	232,620	39,970	89%	98%	84%	27%
Prostate	240,890	33,720	99%	100%	NA	32%
Colorectal	101,340	49,380	64%	90%	68%	11%
Bladder	69,250	14,990	80%	93%	45%	6%
Melanoma	70,230	8,790	91%	99%	65%	16%
Non-Hodgkin's lymphoma	66,360	19,320	67%	81%	71%	58%
Renal cell carcinoma	60,920	13,120	67%	90%	61%	10%
Pancreatic	44,030	37,660	5%	20%	8%	2%
Ovarian	21,990	15,460	46%	93%	71%	31%
Oesophageal	16,980	14,710	16%	34%	17%	3%
Cervical	12,710	4,290	71%	92%	56%	17%

Source: American Cancer Society, National Cancer Institute

Local

Cancer is considered local if it is confined to its organ of origin. For example, in breast cancer, this means the cancer cells have not spread beyond the breast. The prognosis for local disease is usually good, and the first line of treatment is typically surgical removal of the cancerous area. This may be accompanied by irradiation and/or chemotherapy before or after the surgery, the role of each depending upon the type and the stage of the cancer. If used before surgery (neo-adjuvant), the objective is primarily to reduce cancer size and make surgery easier. Post-surgical use (adjuvant) is primarily to kill any unseen or residual cancer cells.

Regional

In regional disease, the cancer cells have spread beyond their organ of origin to nearby areas or to lymph nodes which drain the organ. Lymph nodes contain a collection of immune cells, which filter fluid from the organ before they are returned to the blood circulation. The presence of cancer cells in the lymph nodes draining the organ is usually taken as evidence that the cancer has acquired the ability to spread, and may have spread microscopically to the rest of the body. At this point in time, in order for the cancer to be considered regional and not metastatic, there should not be any clinical evidence of cancer spread to other organs aside from the regional lymph nodes.

Prognosis for regional disease is fair, depending on the type of cancer. Treatment usually involves surgical removal of the cancerous area and regional lymph nodes, plus chemotherapy and/or irradiation.

Metastatic/distant

In the case of metastatic cancer, there is evidence of the spread of cancer cells to other organs, most commonly the liver, lungs, bone and brain. The prognosis is usually poor, with the focus of treatment usually on prolonging life and improving quality of life, rather than cure. Chemotherapy and/or radiation are used in most instances, with surgery used less frequently to remove isolated bulky tumours, often in an attempt to improve symptoms.

The relative size of these categories varies across different types of cancers. In breast cancer, for example, where tumours are often recognised early, the early stage adjuvant market may be twice the size of that for metastatic disease, whereas in lung cancer, the metastatic market accounts for a larger share of drug use. Much of this difference can be accounted for by the ability to diagnose symptoms early – either by obvious lumps or morbidity or through screening programs.

Clinicians' approach to cancer

As cancer is often fatal, oncologists are willing to try many different drugs, usually in combination with one another. In situations where there is little hope of recovery, the objective of treatment is often to prolong survival without significantly reducing the patient's quality of life. Drugs are recommended for first-, second- or third-line treatment, depending on their rate of success relative to other compounds and the impact that they have on a patient's well-being or quality of life. Due to the poor outlook for some patients, if clinicians are aware that a drug undergoing clinical trials has demonstrated some degree of efficacy, they may often be willing try it in an off-label setting in relevant patient groups, even if regulatory approval has yet to be granted.

In earlier stages of treatment (local and regional disease), surgery and the use of radiation are often utilised in combination with high doses of chemotherapy to ensure the cancer does not recur. In this case, physicians are often more willing to reduce a person's quality of life for a short period (while receiving chemotherapy), to ensure longer-term survival and quality of life.

Principles of chemotherapy

The objective of chemotherapy is to kill the cancer cells but leave normal cells unharmed. Unfortunately, the challenge we face is that normal cells and cancer cells originate from the same body, and are therefore common in almost every respect. Hence, unless differences in cellular pathways or distinctive targets can be found, it is extremely difficult to only target cancer cells in treatment.

One key difference is that cancer cells tend to divide more rapidly than normal cells, and cytotoxic chemotherapy agents take advantage of this fact to kill rapidly dividing cells. However, areas of the body which also divide rapidly such as the bone marrow, hair, intestinal lining, and reproductive cells, are also affected by these drugs.

The quest for cancer cell-specific targets has led to the discovery of cancer-specific proteins and the development of both small molecule and antibody-based drugs,

targeting these proteins. These drugs may block the function of the proteins, stop cell division and instruct cell death, or in the case of antibodies, recruit the body's immune system to attack the cancer. A next step forward has been to develop antibodies, attached to chemotherapy drugs, to specifically target the cancer cells with the toxic drug, a so-called magic bullet/ guided missile (e.g. Roche's T-DM1, which contains a chemotherapy drug, emtansine, bound to an antibody targeting HER2).

As cancer cells multiply, they require blood vessels to supply the enlarging tumour with nutrients. A mutation is required to stimulate the release of factors stimulating the creation of new blood vessels (angiogenesis), such as vascular endothelial growth factor (VEGF). One class of drugs focuses on blocking these factors to cut off blood supply to the tumour.

Drugs used to treat cancer

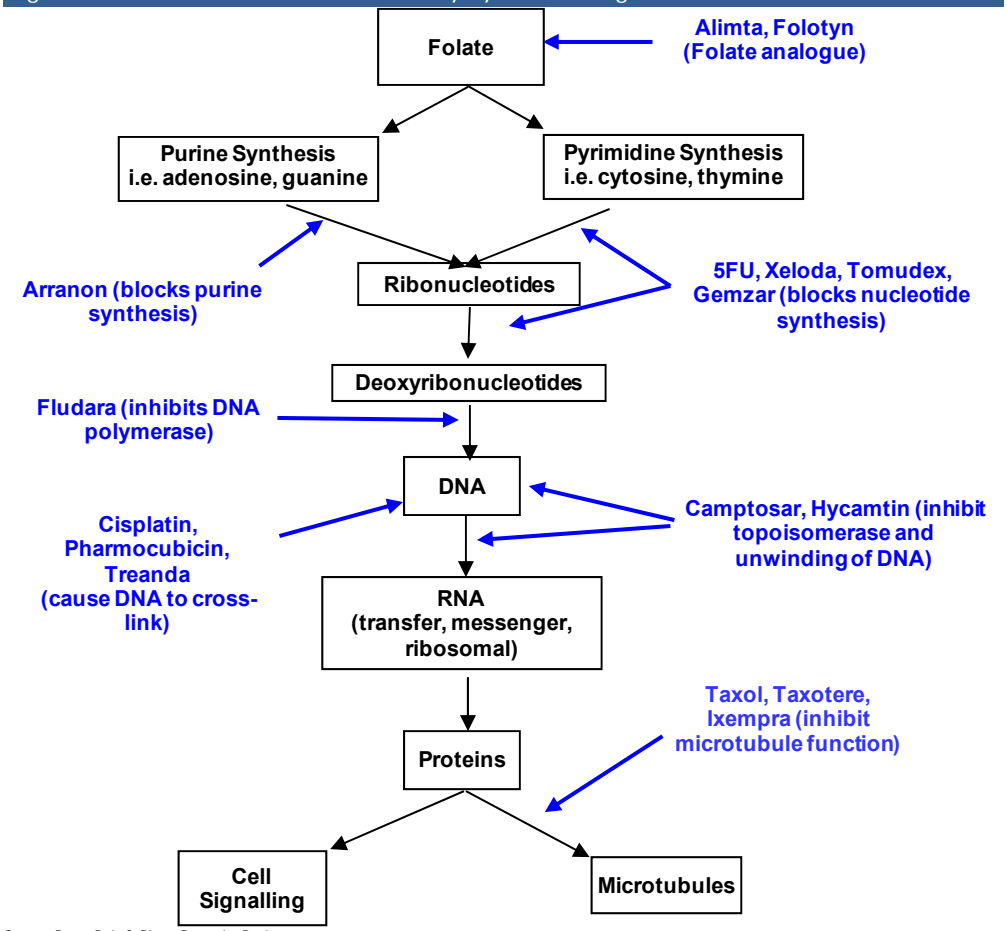
Cancer drugs may be classified by mechanism or alternatively by indication. In this section, we will discuss the common biological pathways. In the subsequent sections, we will focus on the different types of cancers.

Broadly, cancer drugs can be split into four classes: cytotoxics, hormonal therapy, targeted therapies, and supportive therapies. Cytotoxic drugs target the process of DNA replication or cell division, while hormonal therapy is aimed at blocking receptors which promote cell growth in hormone sensitive tumours. Targeted therapies include drugs such as monoclonal antibodies, which target proteins specific to certain types of cancers, or pathways which have gone awry in cancer cells. Supportive drugs are not anti-cancer drugs per se, but play an important role in managing the side-effects of cancer. This group includes drugs which treat the side effects of cytotoxics (e.g. Zofran for nausea). Targeted drugs represent the largest category by value, with 2011 sales of $38bn. Cytotoxics represent the next largest class with sales of almost $17bn, while hormonal drugs had sales of approximately $7bn.

Cytotoxic drugs

Most cytotoxic drugs seek to damage the cell's DNA and trigger cell death or apoptosis, the theory being that the cell's self-destruct mechanism is still intact. Many of these drugs damage the DNA by causing DNA to cross-link. Alternatively, they attempt to corrupt the constituents of DNA itself (i.e. analogues of purines and pyrimidines, i.e. adenosine, guanine, thymidine and cytosine). However, for apoptosis to occur, the p53 gene should be unaffected. Unfortunately, mutation of this gene is common in cancer cells. Other drugs such as the taxanes (Bristol-Myers Taxol and Sanofi's Taxotere) interfere with cell division (mitosis) by blocking microtubule formation (the cellular scaffolding which facilitates cell division).

Figure 294: Mechanisms of action of key cytotoxic drugs



Source: Rang, Dale & Ritter, Deutsche Bank

Figure 294 depicts the stages of cell division and the key action points of some of the more important cytotoxic drugs. Overall, these drugs can largely be divided into several main categories:

- Alkylating agents, which act by forming covalent bonds between DNA, thereby impeding replication. This category includes drugs such as the platinum compounds (e.g. Eloxatin) and Temodar.
- Antimetabolites, which block or subvert the production of DNA, often by interfering with purine and pyrimidine synthesis. Drugs that work in this manner include methotrexate, 5-fluorouracil (5-FU), Xeloda and Gemzar.
- Cytotoxic antibiotics, which prevent mammalian cell division by degrading DNA or inhibiting DNA synthesis. The most frequently used of these are bleomycin and doxorubicin and their derivatives.
- Plant derivatives, such as the taxanes and vinca alkaloids, which disrupt cell division. This category includes products such as Taxotere and Taxol.

Figure 295: Leading cytotoxic drugs

Product	Generic	Company	2011 sales ($)
Alimta	pemetrexed disodium	Eli Lilly	$2.5bn
Xeloda	capecitabine	Roche	$1.5bn
Eloxatin	oxaliplatin	Sanofi	$1.5bn
Taxotere	docetaxel	Sanofi	$1.3bn
Temodar	temozolomide	Merck & Co	$1.3bn
Vidaza	azacitidine	Celgene	$0.7bn
Teysuno	gimeracil; oteracil potassium; tegafur	Otsuka Holdings	$0.5bn
Gemzar	gemcitabine hydrochloride	Eli Lilly	$0.5bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Side effects and resistance

The main limitation of cytotoxic drugs is the side-effects. Cytotoxic drugs are frequently associated with kidney and nerve damage, largely because of the damaging impact of their metabolites. They are also associated with high rates of nausea, as well as negative effects on other fast-dividing cells, such as hair follicles and the gastrointestinal tract. Most significant among these is their effect on the immune system, where low levels of white blood cells (lymphocytes) leave the patient vulnerable to infection.

Beyond side-effects, resistance to treatment is also a problem. Resistance may be primary (present when the drug is first given) or acquired as cancer cells mutate. Consequently, cytotoxic agents are often used in combination to reduce resistance.

Hormonal therapy

In certain cancers, hormones play a major role in promoting cell growth. This is most significant in breast and prostate cancer, where the hormones oestrogen and testosterone play important roles in promoting cell proliferation. Consequently, drugs have been developed that seek to interfere with these pathways, by either reducing oestrogen production in breast cancer, or testosterone production in prostate cancer.

There are essentially four different types of hormonal therapy, which are directed at either reducing the production of the relevant hormone or blocking its action upon cell receptors.

Anti-oestrogens

Drugs in this class, such as AstraZeneca's Nolvadex (tamoxifen), interfere with oestrogen's ability to bind to cell receptors or deplete the number of receptors. In addition to its use in the treatment of advanced or metastatic breast cancer, tamoxifen has also for many years been the standard of care in the adjuvant (i.e. post-surgery) setting.

Figure 296: Leading anti-oestrogens

Product	Generic	Company	2011 Sales ($)
Faslodex	fulvestrant	AstraZeneca	$0.5bn
Nolvadex	tamoxifen citrate	AstraZeneca	$0.4bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Aromatase inhibitors

Aromatase is an enzyme involved in the production of oestrogen from cholesterol. By interfering with this enzyme, aromatase inhibitors block the production of oestrogen. Based on an increasing body of clinical data, the aromatase inhibitors are increasingly replacing tamoxifen as the standard of care in the treatment of metastatic and adjuvant breast cancer.

Figure 297: Leading aromatase inhibitors

Product	Generic	Company	2011 Sales ($)
Femara	letrozole	Novartis	$0.9bn
Arimidex	anastrozole	AstraZeneca	$0.8bn
Aromasin	exemestane	Pfizer	$0.4bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Anti-androgens

The anti-androgens act by either blocking the production of testosterone from cholesterol in the testes or blocking the action of testosterone metabolites on cell receptors, thereby preventing cell division. Medivation's enzalutamide (formerly MDV3100) is the newest anti-androgen that is currently awaiting regulatory approval.

Figure 298: Leading anti-androgens

Product	Generic	Company	2011 Sales ($)
Casodex	bicalutamide	AstraZeneca	$0.6bn
Zytiga	abiraterone acetate	Johnson & Johnson	$0.2bn
Androcur	cyproterone acetate	Bayer	$0.1bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Luteinising hormone-releasing hormone (LHRH) analogues

The production of oestrogen, progesterone and testosterone production are regulated by the hypothalamus, a major hormone-controlling gland located in the brain. LHRH analogues (also known as gonadotropin-releasing hormone or GnRH analogues) inhibit the production of luteinising hormone (LH) and with it, the subsequent production of the main sex hormones.

Figure 299: Leading LHRH analogues

Product	Generic	Company	2011 Sales ($)
Zoladex	goserelin acetate	AstraZeneca	$1.2bn
Leuplin	leuprolide acetate	Takeda	$0.9bn
Lupron	leuprolide acetate	Abbott Laboratories	$0.8bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

17 α hydroxylase (CYP17) inhibitor

While LHRH analogues or anti-androgens may initially be effective in slowing the growth of testosterone dependent tumours, there remains escape pathways such as the CYP17 enzyme, by which testosterone can still be produced in the body (despite medical and surgical castration). These tumours may therefore continue to grow despite being subjected to hormonal therapy. Drugs such as Johnson & Johnson's Zytiga (FDA/EMA approval in 2011) acts as a selective inhibitor of CYP17, which blocks this escape pathway as well as the production of testosterone. However, CYP17 blockade also results in a build-up of adrenocorticotropic hormone (ACTH), leading to hyperaldosteronism and adverse effects such as hypertension and hypokalemia. Giving patients low doses of prednisolone concurrently was found to reduce these symptoms by a feedback loop to reduce the secretion of ACTH.

Figure 300: 17 α hydroxylase (CYP17) inhibitor

Product	Generic	Company	2011 Sales ($)
Zytiga	abiraterone acetate	Johnson & Johnson	$0.2bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Targeted therapy

The fastest-growing class of cancer drugs over the past few years is the targeted therapies. Included in this class is Roche's blockbuster Mabthera/Rituxan, a genetically engineered antibody that binds to a specific antigen found on more than 90% of non-Hodgkin's lymphoma (NHL) B-cells and facilitates selective cell death. Novartis' Glivec, launched in 2001, is likewise a highly targeted therapy that has produced dramatic results in patients with chronic myeloid leukaemia (CML). These drugs employ a more targeted approach to attack cancer cells which is often associated with less severe side-effects compared to traditional cytotoxic drugs. However, this also implies that they may have more limited application across different tumour types. This has not hindered sales of these drugs, which have prices in excess of $30,000 per patient per year. We will briefly elaborate on several important targets of this class.

CD20

CD20 is a phosphoprotein found on the surface of antibody-secreting lymphocytes (B-cells). As such, it is a logical target for drugs treating B-cell lymphomas, B-cell chronic lymphocytic leukemia (CLL) and hairy-cell leukemia. Roche's Rituxan (rituximab) was the first anti-CD20 monoclonal antibody in this class and is approved for use in CLL, Non-Hodgkin lymphoma and rheumatoid arthritis. GlaxoSmithKline and Genmab's Arzerra (ofatumumab) received approval in October 2009 for use in 2nd-line CLL (following the failure of other therapies). Roche is developing a follow-on next generation anti-CD20 monoclonal antibody, ocrelizumab, which is currently in Phase III studies.

Tyrosine kinases

Tyrosine kinases are a class of enzymes involved in cell signaling that act by phosphorylation of tyrosine (transfers a phosphate group to the amino acid, tyrosine). This causes a conformational change in the protein of which it is a constituent. Tyrosine kinases play an important part in numerous signalling pathways, e.g. cell-to-cell signalling, and are involved in cell division. Some forms of cancer cells have gene mutations that result in the production of malfunctioning tyrosine kinase enzymes, which are permanently actived and promote uncontrolled cell replication. Many tyrosine kinase inhibitors have been developed, which target the malfunctioning enzyme in the pathway and have utility in more than one cancer. Ideally, to avoid eventual resistance (which develop through 'escape pathways'), tyrosine kinase inhibitors should work downstream in a signal transduction pathway. Novartis' Gleevec/Glivec (imatinib), Pfizer's Sutent (sunitinib) and Bayer's Nexavar (sorafenib) are examples of drugs in this category.

Epidermal growth factor receptor (EGFR)

The epidermal growth factor receptor is part of the ErbB class of receptors, and mutations resulting in over-activity may lead to uncontrolled cell division. Drugs have been developed which block the receptor site or inhibit the EGFR-associated tyrosine kinase, effectively blocking stimulation of the pathway. Examples of this class of drugs include Bristol-Myers Squibb/Eli Lilly/Merck's Erbitux (cetuximab), Roche's Tarceva (erlotinib) and AstraZeneca/Teva's Iressa (gefitinib).

Vascular endothelial growth factor (VEGF)

VEGF is a factor which stimulates the growth of new blood vessels (angiogenesis), and is normally secreted to repair blood vessels following injury or bypass blocked vessels. Cancers need a blood supply to grow and so up-regulate VEGF to create their own blood supply. Roche's targeted antibody, Avastin, has received approval as first-line treatment for several metastatic solid tumour types (e.g. colorectal cancer, non-small-cell lung cancer, renal cell cancer and glioblastoma). Sanofi/Regeneron's Zaltrap also targets several tumour types and was approved by the FDA in August 2012 for use in colon cancer, following a priority review.

Human epidermal growth factor receptor 2 (HER2/neu)

HER2/neu is a member of the EGFR group, and hence is a tyrosine kinase-linked receptor involved in the signalling pathway for cell division and differentiation. Over-expression of this receptor is seen in c.25% of breast cancers, and is associated with more aggressive cancer and a worse prognosis. Roche's Herceptin (trastuzumab) was the first monoclonal antibody developed against the HER2 receptor, blocking it and the associated overstimulation of cell division. In addition, GlaxoSmithKline's Tykerb, a small molecule targeted against the HER2 pathway, received FDA approval in 2007. A new formulation of Herceptin has been developed, T-DM1, which has a chemotherapy drug linked to trastuzumab to achieve a targeted delivery of chemotherapy. A biologic license application will be filed with the FDA in 2H 2012. Roche also recently received approval of a second-generation HER2 antibody, Perjeta (pertuzumab), which acts via a different mechanism of action (in blocking the activation of HER2 by inhibiting dimerisation of HER2). Perjeta was approved by the FDA in June 2012 for in combination with Herceptin and Taxotere for treatment of patients with HER2 positive metastatic breast cancer.

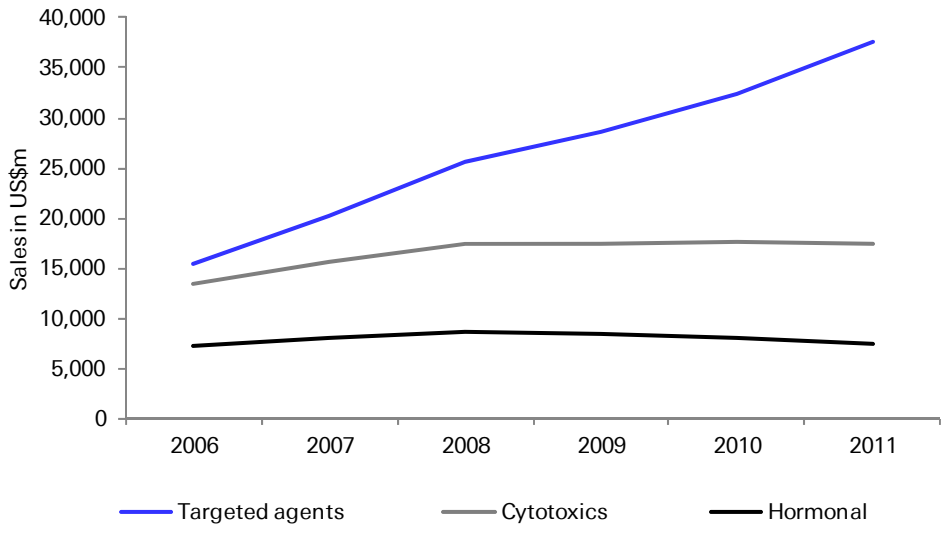
Figure 301: Leading targeted oncology drugs

Product	Generic	Company	2011 Sales ($)
Rituxan	rituximab	Roche	$6.8bn
Avastin	bevacizumab	Roche	$6.0bn
Herceptin	trastuzumab	Roche	$5.9bn
Glivec	imatinib	Novartis	$4.7bn
Revlimid	lenalidomide	Celgene	$3.2bn
Tarceva	erlotinib	Roche	$1.4bn
Velcade	bortezomib	Johnson & Johnson	$1.3bn
Erbitux	cetuximab	Bristol-Myers Squibb /Merck KGaA	$1.9bn
Sprycel	dasatinib	Bristol-Myers Squibb	$0.8bn
Tasigna	nilotinib	Novartis	$0.7bn
Velcade	bortezomib	Takeda	$0.7bn
Iressa	gefitinib	AstraZeneca	$0.6bn
Afinitor	everolimus	Novartis	$0.4bn
Tykerb	lapatinib	GlaxoSmithKline	$0.4bn
Yervoy	ipilimumab	Bristol-Myers Squibb	$0.4bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Sales

Figure 302: Sales of oncology drugs



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 303: Sales of oncology drugs ($ m)

Class	2006	2007	2008	2009	2010	2011
Targeted agents	15,499	20,308	25,681	28,620	32,454	37,688
Cytotoxics	13,537	15,551	17,438	17,377	17,631	17,335
Hormonal	7,238	8,143	8,648	8,454	8,047	7,406

Source: Company data, Deutsche Bank estimates, EvaluatePharma

Supportive therapies

Due to the serious side effects caused by most cancer chemotherapies, there is significant demand for drugs which alleviate these symptoms. These agents broadly fall into four categories: erythropoietins, cytokines, anti-emetics and bisphosphonates. Erythropoietins (EPOs) are used for the treatment of chemotherapy-induced anaemia (red blood cell depletion) as well as anaemia associated with end-stage renal disease. In the cytokine family, key drugs include Amgen's Neupogen and its follow-on product, Neulasta, both of which are indicated for the treatment of neutropenia (white blood cell depletion). Other products in this category include Neumega for the treatment of thrombocytopenia (platelet depletion). The anti-emetics, including GlaxoSmithKline's Zofran and Roche's Kytril, help treat chemotherapy-induced nausea. Finally, Novartis' Zometa and others comprise the bisphosphonate class, used for the treatment of hypercalcemia of malignancy, or to reduce fracture and bone pain associated with bone metastases.

Figure 304: Sales of key supportive therapies (excluding erythropoietins)

Product	Generic	Company	2011 Sales ($)
Neulasta	pegfilgrastim	Amgen	$4.0bn
Zometa	zoledronic acid	Novartis	$1.5bn
Neupogen	filgrastim	Amgen	$1.3bn
Fosamax	alendronate sodium	Merck & Co	$0.9bn
Boniva	ibandronate sodium	Roche	$0.8bn
Actonel	risedronate sodium	Warner Chilcott	$0.8bn

Source: Company data, Deutsche Bank estimates, EvaluatePharma

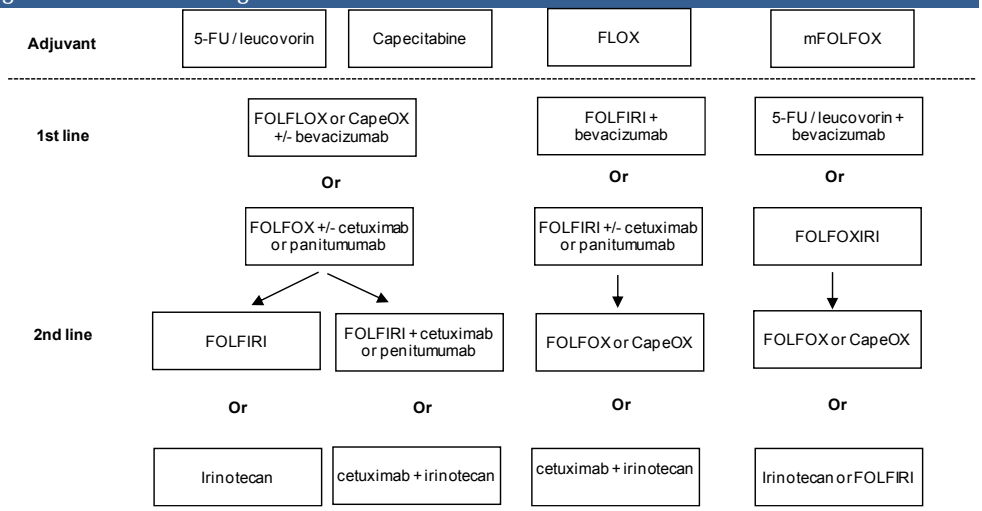
Colorectal cancer

Colorectal cancer (CRC) currently represents the second leading cause of cancer-related deaths in the US. As the name suggests, this type of cancer comprises tumours that develop either in the colon (also known as the large intestine) or the rectum. Ninety-five percent of colorectal tumours are adenocarcinomas, meaning they develop from glands along the lining of the colon and rectum. Less common tumours which may occur in the colon include gastrointestinal stromal tumours (GIST), which develop from specialised cells (interstitial cells of Cajal) found in the wall of the colon, and carcinoid tumours which develop from hormone-producing cells in the intestine.

The relative survival for CRC patients whose cancer has been treated at an early stage is 90%. However, only c.40% of tumours are diagnosed at this stage. Once the cancer has spread to the nearby organs or lymph nodes, the five-year survival rate falls to 70%. If the cancer has spread (metastasised) to distant organs and lymph nodes, the five-year survival rate is only around 10%.

The primary drugs and drug regimens used to treat CRC are shown in Figure 305 and Figure 306. In the metastatic setting, there are two alternative first-line regimens which are used fairly equally. These are referred to as FOLFOX (Eloxatin + 5-fluorouracil + leucovorin) and FOLFIRI (Camptosar + 5-fluorouracil + leucovorin). However, the choice of one first-line treatment over the other implies a different course of second- and third-line options.

Figure 305: Treatment guidelines for colorectal cancer



Source: National Comprehensive Cancer Network (NCCN)
FLOX = 5-FU/leucovorin + oxaliplatin (Eloxatin), mFOLFOX = oxaliplatin (Eloxatin) + leucovorin/5FU, FOLFIRI = leucovorin + 5-FU + irinotecan, CapeOX = capecitabine + oxaliplatin

Figure 306: Drugs for colorectal cancer

Name	Generic	Adjuvant	1st line	2nd line	3rd line	Comments
Eloxatin	oxaliplatin	x	x	x		
Camptosar	irinotecan	x	x			
Avastin	bevacizumab	x	x	x		
Xeloda	capecitabine	x	x			
Erbitux	cetuximab		x	x		
Vectibix	panitumumab			x		
Zaltrap	Ziv-aflibercept			x		

Source: Company data

Lung cancer

Lung cancer is the second most common type of cancer found in both males and females, and is by far the leading cause of cancer-related death. More people die of lung cancer than of colon, breast and prostate cancers combined. Of the different types of lung cancer, non-small-cell lung cancer (NSCLC) accounts for around 85-90% of all cases, with the balance caused by small-cell lung cancer (SCLC). SCLC is so named because of the small cells which comprise this cancer, and is usually seen in smokers. SCLC is aggressive and often widespread by the time of diagnosis, such that treatment is usually palliative and limited to chemotherapy and/or radiation. NSCLC, in contrast, is sometimes detected early enough such that curative surgical resection may be possible.

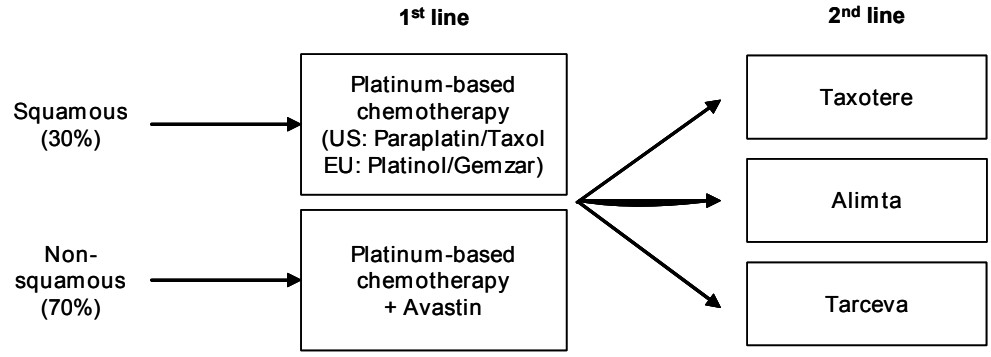
The following subtypes account for the majority of tumours in NSCLC:

- **Squamous cell carcinomas** – These account for around 30% of NSCLC cases and are often centrally located. They are generally associated with a history of smoking and tend to be slow growing.
- **Adenocarcinomas** – These account for 40% of NSCLC cases and are usually found at the periphery of the lungs. Adenocarcinomas typically have a worse prognosis than squamous cell tumours.
- **Other non-squamous cancers** – These account for the remainder of cases and include large-cell cancer. These may occur in any part of the lung, and tend to be aggressive. They are therefore associated with a worse prognosis.

Nearly 60% of people diagnosed with lung cancer will die within one year, and 75% will die within two years. For patients whose tumours are diagnosed before they have spread, the five-year survival rate is roughly 50%. However, only 15% of patients are diagnosed at this stage, and the five-year survival rate across all patients is 16%.

The primary drug regimens used to treat NSCLC are shown in Figure 307 and Figure 308. Given the small number of patients diagnosed at an early stage and the lack of conclusive data supporting adjuvant treatment, the focus of chemotherapy is in the metastatic setting. First-line treatment generally relies on a platinum-based compound together with another cytotoxic agent, often in combination with radiation therapy. However, the preferred combination of drugs differs in the US and Europe, with American oncologists preferring the combination of carboplatin and Taxol, whereas European clinicians tend to use cisplatin and Gemzar. In addition, Avastin is increasingly used in combination with carboplatin /Taxol in a first-line setting.

Figure 307: Treatment guidelines for NSCLC



Source: National Comprehensive Cancer Network (NCCN)

Figure 308: Drugs approved for lung cancer

		---------- NSCLC ----------				
Name	Generic	1st line	2nd line	3rd line	SCLC	Comments
Paraplatin*	carboplatin	x			x	
Platinol*	cisplatin	x			x	
Taxol*	paclitaxel	x				
Taxotere*	docetaxel	x	x			
Gemzar*	gemcitabine	x				
Alimta	pemetrexed	x	x			
Avastin	bevacizumab	x				
Tarceva	erlotinib		x			
Iressa	gefitinib			x		
Hycamtin*	topotecan			x		

Source: Company data
**Off-patent*

Breast cancer

Breast cancer is the most common cancer among women, with more than 1 million new cases diagnosed worldwide each year. Fortunately, due to the increasing implementation of screening programs, breast cancers are increasingly diagnosed at an early stage when the tumour is still resectable and cure rates are high. Frequent early detection also implies that the adjuvant (pre- and post-surgery chemotherapy) market accounts for a significant portion the drugs used in breast cancer. We have attempted to summarise the most frequent treatment protocols in both of these settings below.

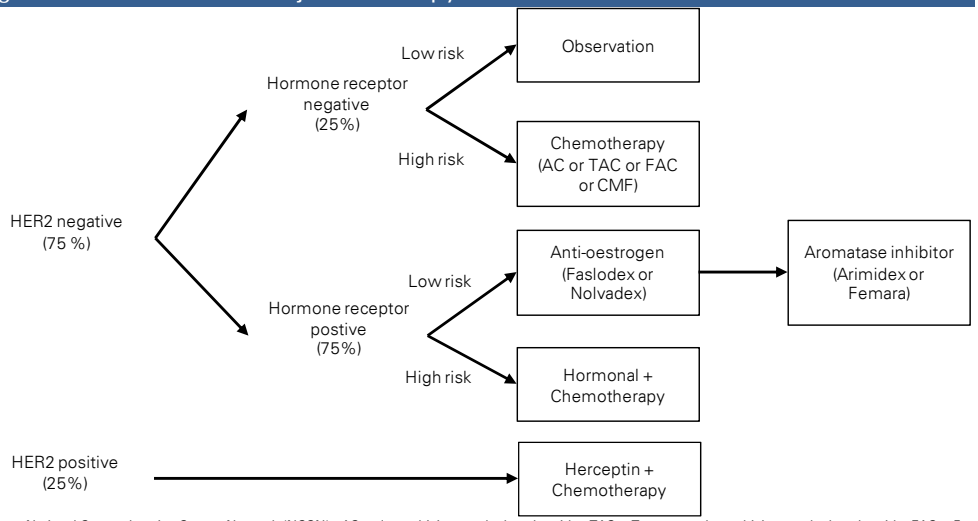
Adjuvant

Approximately 70% of patients with breast cancer would have been diagnosed at an early stage. The choice of an appropriate drug regimen is dependent primarily on a patient's hormone-receptor status and whether cancer cells over-express a protein known as HER2. Herceptin, which targets the HER2 receptor, has become the standard of care in HER2+ patients (c.25% of breast cancers). Clinical trials have demonstrated a significant improvement in overall survival with Herceptin in high-risk, HER2+ breast cancer, independent of hormone receptor status.

Amongst patients who do not over-express HER2, roughly two-thirds are likely to have tumours which are oestrogen- and/or progesterone-receptor positive (ER-positive or PR-positive). In these patients, hormones are involved in the promotion of tumour growth, and thus treatment primarily relies on drugs that block hormonal stimulation of the cancer. Historically, AstraZeneca's Nolvadex (tamoxifen) was considered the first choice adjuvant treatment for hormone receptor-positive breast cancer, though aromatase inhibitors (e.g. Arimidex, Femara) may possibly offer a greater reduction in the risk of cancer recurrence.

In patients that are hormone receptor-negative and HER2 negative, but that are at high risk of cancer recurrence (as well as some patients who are hormone receptor-positive and high risk), physicians may prescribe a course of cytotoxic chemotherapy usually lasting three to six months. Traditionally, these have been doxorubicin-based regimens, with recent data supporting the addition of one of the taxanes (Taxol or Taxotere).

Figure 309: Treatment for adjuvant therapy in breast cancer



Source: National Comprehensive Cancer Network (NCCN) AC = doxorubicin + cyclophosphamide; TAC = Taxotere + doxorubicin + cyclophosphamide; FAC = 5-FU + doxorubicin + cyclophosphamide; CMF = 5-FU + cyclophosphamide + methotrexate

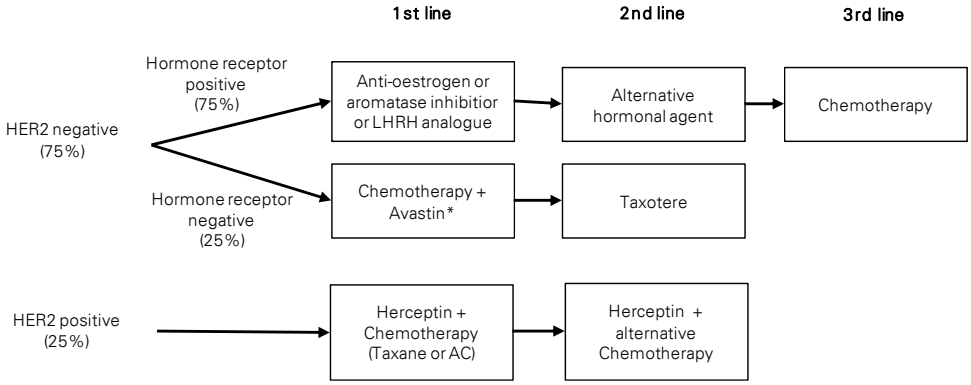
Neoadjuvant

Sometimes, hormonal drugs (Nolvadex, Arimidex, Femara) and cytotoxics (Taxotere) are used in the neoadjuvant setting (i.e. before surgery). Administration of these drugs has been shown to shrink tumours ahead of surgery and increase the chances of allowing a breast-conserving procedure (i.e. lumpectomy, partial mastectomy).

Metastatic

Treatment of metastatic or late-stage breast cancer varies according to a number of factors, including a patient's tumour type, disease prognosis, the presence of hormonal receptors and HER2 receptor status. Patients that are hormone receptor-positive may be treated with hormonal therapy, while those that are hormone receptor-negative may be treated with chemotherapy. Importantly, hormonal therapy and chemotherapy are generally not combined in the metastatic setting, and single agents are preferable to combination chemotherapy. This is because in cases of metastatic cancer, combination chemotherapy is associated with an increase in toxicity with little survival benefit over single agents. Additionally, some 25-30% of metastatic patients with tumours that overexpress HER2 should receive Herceptin in combination with chemotherapy. Bisphosphonates such as Zoledronic acid are also recommended to reduce the risk of pathological fractures associated with bony metastases. The use of Avastin in breast cancer has a modest effect, with approval in Europe together with chemotherapy. However, the FDA Advisory Committee voted to rescind approval in the US as the benefit seen in initial studies failed to be replicated in subsequent studies.

Figure 310: Treatment for metastatic breast cancer



*Source: DB estimates, *Approved EU, FDA AdCom voted against use*

Figure 311: Drugs approved for breast cancer

Name	Generic	Adjuvant	1st line	2nd line	Comment
Taxol*	paclitaxel	x		x	
Taxotere*	docetaxel	x		x	
Alimta	premetrexed	x	x		
Gemzar*	gemcitabine	x			
Xeloda	capecitabine		x		
Abraxane	Paclitaxel /albumin		x		
Ellence*	epirubicin	x			
Avastin**	bevacizumab		x	x	
Afinitor	everolimus			x	Hormone receptor+
Nolvadex*	tamoxifen	x	x		Hormone receptor+
Arimidex*	anastrazole	x	x	x	Hormone receptor+
Femara*	letrozole	x	x	x	Hormone receptor+
Aromasin*	exemestane	x		x	Hormone receptor+
Faslodex	fulvestrant			x	Hormone receptor+
Zoladex	goserelin			x	Hormone receptor+
Herceptin	trastuzumab	x	x	x	HER2+ tumour

*Source: Company data, *Off-patent, **EU approval*

Prostate cancer

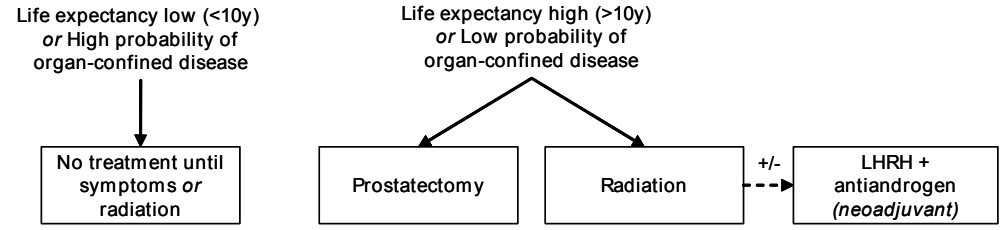
Prostate cancer is one of the most common cancers occurring in men. The disease is rare in people under the age of 40, but the risk rises significantly with age. More than 99% of prostate cancers develop from gland cells, giving rise to adenocarcinomas, most of which are slow-growing. In fact, the American Cancer Society suggests that 70-90% of men have cancer in their prostate by age 80, but the majority remain undiagnosed and asymptomatic.

Early stage

Because prostate cancer often grows very slowly and appears with advanced age, many men remain undiagnosed and may never suffer its ill effects. Given the side effects associated with treatment, and that the 10-year survival rate for localised tumours is over 80%, doctors and patients may opt for a period of 'watchful waiting.'

However, in the event the patient still has significant life expectancy (>10 years), the first course of treatment is a radical prostatectomy (removal of the prostate) or radiation therapy. A course of ADT (Androgen Deprivation Therapy) using a luteinising hormone releasing hormone (LHRH) agonist together with an anti-androgen may also be used prior to and during radiotherapy to reduce the risk of disease recurrence. This combination is designed to achieve maximum androgen deprivation by blocking androgen production via the LHRH analogue and blocking androgen activity via the anti-androgen.

Figure 312: Treatment of early-stage, localised prostate cancer



Source: National Comprehensive Cancer Network (NCCN)

Metastatic

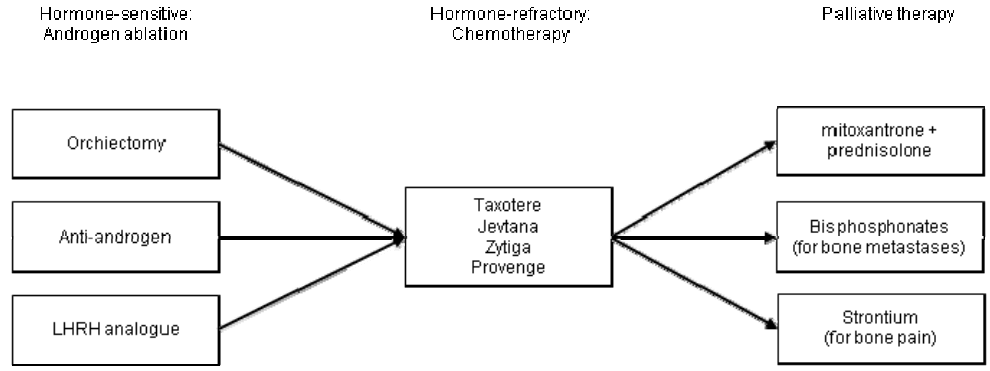
Although survival rates for patients with early-stage prostate cancer are very high, some patients will develop advanced or metastatic disease. Traditionally, first-line therapy focuses on androgen deprivation via either orchiectomy (surgical removal of the testes) or medical castration using an LHRH analogue, often in combination with a non-steroidal anti-androgen, e.g. Casodex. While orchiectomy is arguably the more cost-efficient method, many patients prefer treatment with an LHRH analogue, as the surgical procedure is non-reversible and carries a significant psychological burden.

While some 80% of patients initially respond to hormonal therapy, the disease eventually progresses in most cases. Once the disease progresses despite hormonal therapy, the patient is considered to have hormone-refractory prostate cancer (HRPC). In these patients, Taxotere-based regimes are the preferred first-line treatment. Recently, there have been a number of advances in therapy for prostate cancer, including Dendreon's immune therapy agent, Provenge, a prostate cancer vaccine which has been approved for first line use in HRPC. In addition, Sanofi's cytotoxic agent Jevtana and Johnson & Johnson/ BTG's CYP17 inhibitor Zytiga have also been approved for second-line treatment in patients that have received Taxotere-based chemotherapy. Medivation's enzalutamide (formerly MDV3100) is another new anti-

androgen that demonstrated success in second line treatment and is currently awaiting regulatory approval.

For metastatic prostate cancer with painful bone metastases, mitoxantrone with prednisolone has shown some palliative benefit in patients, though its benefit on survival is debatable. It was the default treatment for patients with HRPC prior to Taxotere. Systemic radiotherapy with strontium-89 and samarium-153 may be an option for patients with widespread bony metastases who are unable to tolerate localised radiotherapy. Bisphosphonates such as Zoledronic acid are also recommended to reduce the risk of pathological fractures in patients with bone metastases.

Figure 313: Treatment of metastatic prostate cancer



Source: National Comprehensive Cancer Network (NCCN), Deutsche bank

Figure 314: Drugs approved for prostate cancer

Name	Generic	Early-stage	Metastatic (hormone sensitive)	Metastatic (hormone refractory)	Comment
Lupron	leuprolide	x			
Eligard	leuprolide	x			
Zoladex	goserelin	x	x		
Casodex*	bicalutamide	x			
Taxotere*	docetaxel		x		
Jevtana	cabazitaxel		x		2nd line for failure/non-responders
Zytiga	Abiraterone			x	2nd line for failure/non-responders
Provenge	Sipuleucel-T			x	

Source: Company data

Oncology pipeline

Oncology is one of the biggest areas of focus for pharmaceutical R&D. Numerous drugs in development aim to improve upon existing products or are designed to offer new mechanisms to treat the disease. Major development projects are listed in Figure 315 to Figure 319 according to cancer type.

Figure 315: Selected development candidates for colorectal cancer

Name	Mechanism	Company	Status
Regorafenib	Oral multi-kinase inhibitor	Bayer	Filed
Ramucirumab	Targets VEGFR-2	Eli Lilly	Phase III

Source: Company information

Figure 316: Selected development candidates for non-small cell lung cancer

Name	Mechanism	Company	Status
dacomitinib	Pan-HER inhibitor	Pfizer	Phase III
necitumumab	Anti-EGFR monoclonal antibody	Eli Lilly/BMS	Phase III
MAGE-A3	recombinant	GlaxoSmithKline	Phase III
onartuzumab	Met inhibitor	Roche	Phase III
iniparib	PARP1 inhibitor	Sanofi	Phase III
Ramucirumab	Targets VEGFR-2	Eli Lilly	Phase III

Source: Company information

Figure 317: Selected development candidates for breast cancer

Name	Mechanism	Company	Status
trastuzumab-DM1	anti-HER2 Ab + chemotherapy	Roche	Awaiting filing
pertuzumab	HER2 dimerisation inhibitor	Roche	Filed EU/Approved US

Source: Company information

Figure 318: Selected development candidates for prostate cancer

Name	Mechanism	Company	Status
Enzalutamide	androgen receptor blocker	Medivation/Astellas	Filed
Alpharadin	α-emitting radium	Algeta/Bayer	Awaiting filing
Orteronel	Anti-androgen	Takeda	Phase III
Prostvac	Therapeutic vaccine	Bavarian Nordic	Phase III
Custirsen	Clusterin blocker	OncoGenex	Phase III

Source: Company information

Figure 319: Selected development candidates for other cancers

Name	Mechanism	Company	Status	Indication
bosutinib	Abl and src family kinase inhibitor	Pfizer	Filed	CML
inotuzumab ozogamicin	CD22-targeted cytotoxic agent	Pfizer	Phase III	NHL
ridaforolimus	mTOR inhibitor	Merck	Phase III/FDA CRL	Sarcoma
vintafolide	alkylating agent	Merck/Endocyte	Phase III	Ovarian cancer
Enzastaurin	Protein kinase inhibitor	Eli Lilly	Phase III	Large B-Cell Lymphoma
Ramucirumab	Targets VEGFR-2	Eli Lilly	Phase III	Solid tumours
Elotuzumab	Targets CS1	Bristol-Myers Squibb	Phase III	Multiple myeloma
trametinib	MEK 1/2 inhibitor	GlaxoSmithKline	Phase III	Metastatic melanoma
Debrafenib	BRAF protein kinase inhibitor	GlaxoSmithKline	Phase III	Metastatic melanoma
MAGE-A3	recombinant	GlaxoSmithKline	Phase III	Melanoma/Bladder cancer
Tykerb	Tyrosine kinase inhibitor	GlaxoSmithKline	Phase III	Head & neck/gastric cancer
Jakavi	JAK inhibitor	Novartis	Filed EU/Approved US	Myelofibrosis
Afinitor/Votubia	mTOR inhibitor	Novartis	Phase III	HCC/GI and lung NET/lymphoma
Avastin	anti-VEGF	Roche	Phase III	Ovarian cancer
obintuzumab	anti-CD-20	Roche	Phase III	NHL/CLL
SAR302503	JAK-2 inhibitor	Sanofi	Phase III	Myelofibrosis
ombrabulin	vascular disrupting agent	Sanofi	Phase III	Sarcoma

Source: Company information

Anaemia (erythropoietin)

- Global sales of erythropoietin totaled c.$8.4bn in 2011.
- Two key sub-sectors: renal dysfunction and cancer anaemia.
- Growth has slowed due to restrictions in cancer and EU biosimilars.
- Major players are Amgen, Johnson & Johnson, and Roche/Chugai.

Physiology

Anaemia is a deficiency of red blood cells, which can lead to a lack of oxygen-carrying ability, causing fatigue and other symptoms such as shortness of breath and heart palpitations. The deficiency occurs either through the reduced production or an increased loss of red blood cells. Red blood cells are manufactured in the bone marrow and have a life expectancy of approximately four months. To produce red blood cells, the body needs (among other things) iron, vitamin B12 and folic acid. If there is a lack of one or more of these nutrients, anaemia will develop. Most cases of iron deficiency in children are caused by a poor diet containing little iron. In adults, however, it is most commonly caused by a loss of blood. Unsurprisingly, anaemia is more common in women due to blood loss during the menstrual cycle and the increased requirement for iron during pregnancy.

Chronic anaemia, on the other hand, may result from malfunctioning kidneys or damage to the bone marrow. Specifically, the kidneys secrete a hormone called erythropoietin (EPO), which in turn stimulates the bone marrow to manufacture red blood cells. Hence, patients with failing kidneys, such as those requiring renal dialysis, or patients receiving bone marrow-depleting chemotherapy typically experience severe anaemia. The majority of patients with chronic anaemia requiring treatment are those with damaged or failing kidneys. In the US, for example, approximately 200,000 people undergo dialysis and are potential candidates for therapy.

Pharmacological treatment

Mild or episodic anaemia arising from iron deficiency can be simply treated by dietary changes, including iron supplementation, while emergency cases may require a blood transfusion. However, for the treatment of chronic anaemia, especially when it is the result of kidney malfunction or the side effect of cancer treatment, one option is to administer injections of biosynthetically manufactured EPO.

The main manufacturers of EPO are Amgen, Johnson & Johnson, Roche and the latter's affiliate, Chugai. Since 2001, Amgen has also marketed its longer-acting modified EPO, Aranesp (darbepoietin alpha), in the US and Europe for anaemia resulting from cancer chemotherapy and in dialysis patients. Aranesp differs from 'plain' EPO in having two of the 165 amino acids substituted and in its degree of glycosylation (it has five carbohydrate chains attached vs. EPO's three, hence its higher molecular weight). Aranesp is priced at a small premium to the other EPOs and is injected once a week, whereas the other EPOs are injected three times a week.

Outside the US, Roche launched Mircera in 2007, a methoxy-PEG-form of erythropoietin beta, which is longer acting and can be administered once every two

weeks. Roche cannot yet launch Mircera in the US as it is deemed to contravene Amgen's patents; an agreement allows launch in mid-2014.

Controversy

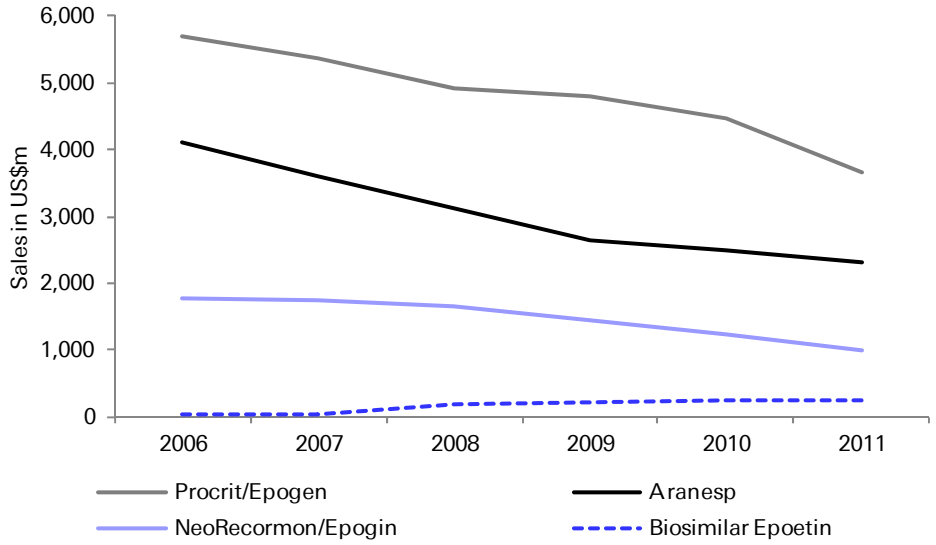
Sales in this class were affected when reports arose in 2004 suggesting that use of EPO in cancer was associated with a lower survival rate due to an increased incidence of fatal thromboembolic events and tumour progression. This led in 2007 to the FDA mandating a black-box warning of these risks, which were particularly heightened in patients who were treated to a target haemoglobin of >12g/dL. The Centers for Medicare and Medicaid Services followed suit by restricting reimbursement for EPO in patients without renal disease.

In the latest guidelines issued by the American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) in 2010, the use of EPO in chemotherapy-associated anaemia is cautiously supported if haemoglobin is lower than 10 mg/dl, but usage of EPO to treat cancer-associated anaemia is discouraged in the absence of chemotherapy.

Sales

With the patent expiry of erythropoietin alfa in 2004, the EMA has taken the lead in approving biosimilars, with EPOs from Sandoz, Hexal, Medice, Hospira and Stada receiving approval for sale in the EU. Worldwide sales of branded erythropoietin have declined at an annualized rate of 7% since their peak in 2006, and now total $8.4bn for 2011.

Figure 320: Sales of key erythropoietins



Source: Company data, Deutsche Bank estimates, EvaluatePharma

Figure 321: Sales of key erythropoietins ($ m)

Name	Company	2006	2007	2008	2009	2010	2011
Procrit/ Epogen	Amgen/Johnson & Johnson	5,691	5,374	4,916	4,814	4,458	3,663
Aranesp	Amgen	4,121	3,614	3,137	2,652	2,486	2,303
NeoRecormon/ Epogin	Roche/Chugai	1,778	1,747	1,642	1,440	1,235	1,013
Biosimilar Epoetin	Various	27	30	202	214	243	250

Source: Company data

Orphan genetic diseases

- Over 5,500 rare diseases identified but only a minority of patients is treated.
- Global sales of enzyme replacement therapies totalled c.$4bn in 2011.
- Leading companies include Sanofi (through its Genzyme business) and Shire.

According to GlaxoSmithKline, more than 5,500 rare diseases (typically affecting <10,000 patients globally) have been identified, many of these are genetic in origin and less than 10% of patients are treated. Despite the rarity of each condition, collectively these rare diseases add up to a potential 6-8% of the population. Not all rare diseases are treatable and the prognosis varies between diseases. One area of significant medical progress however has been the use of Enzyme Replacement Therapies (ERTs) which are used to treat rare diseases where the patient lacks a functional gene encoding for a critical enzyme or protein. Left alone or untreated, these diseases frequently result in significant morbidity and in some cases in early death.

The ERT market

The ERT market is currently worth around $4bn. It is typified by small patient numbers, a high cost of treatment (typically >$100,000 pa), limited resistance to reimbursement by payers (as these rare diseases are generally manifested in childhood and are serious in nature), growing demand (as children and adolescents receiving treatment will typically live longer and diagnosis is improving), high compliance, orphan drug exclusivity protection (seven years in the US, ten years in the EU), limited competition, and low marketing costs. Treatment usually involves a regular infusion of enzymes to replace what the body is not able to produce.

The market leader is Sanofi (c.63% market share), followed by Shire (c.22% market share). Manufacturing issues since 2009 at Genzyme (acquired last year by Sanofi) disrupted supplies of its leading ERTs for Gaucher and Fabry disease, Cerezyme and Fabrazyme. This led to patients having to receive reduced doses and in some cases to treatment being reserved only for existing rather than new patients. Competitor Shire consequently captured substantial market share although as of 1H 2012 Sanofi has resumed full supply of its affected products, following approval of a new US plant.

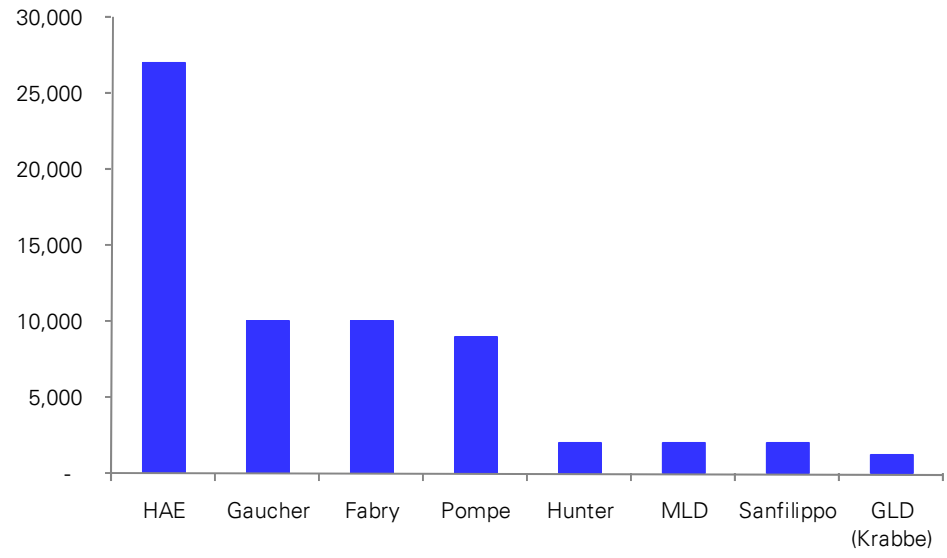
Figure 322: Orphan genetic disease market ($ m)

Product name	Generic name	Company	Disease	2011 Sales ($ m)
Cerezyme	Imiglucerase	Sanofi	Gaucher's disease	885
Myozyme/Lumizyme	alglucosidase alfa	Sanofi	Pompe disease	591
Replagal	agalsidase alfa	Shire	Fabry disease	591
Elaprase	idursulfase	Shire	Hunter Syndrome	465
Fabrazyme	agalsidase beta	Sanofi	Fabry disease	256
VPRIV	velaglucerase	Shire	Gaucher's disease	256
Cinryze	C1 esterase inhibitor (human)	ViroPharma	Hereditary angioedema	251
Naglazyme	galsulfase	Biomarin	Maroteaux-Lamy Syndrome	225
Aldurazyme	laronidase	Sanofi/Biomarin	Hurler Syndrome	205
Zavesca	miglustat	Actelion	Gaucher's disease	77
Firazyr	icatibant acetate	Shire	Hereditary angioedema	33
Kalbitor	ecallantide	Dyax	Hereditary angioedema	23
Elelyso	taliglucerase	Protalix/Pfizer	Gaucher's disease	0

Source: Company data, Deutsche Bank

Figure 323 sets out the most prevalent single-mutation inherited disorders in which ERT may be used.

Figure 323: Orphan genetic disease prevalence (patients globally)



Note: HAE, hereditary angioedema; MLD, metachromatic leukodystrophy; GLD, globoid cell leukodystrophy
Source: Shire HGT presentation , November 2008

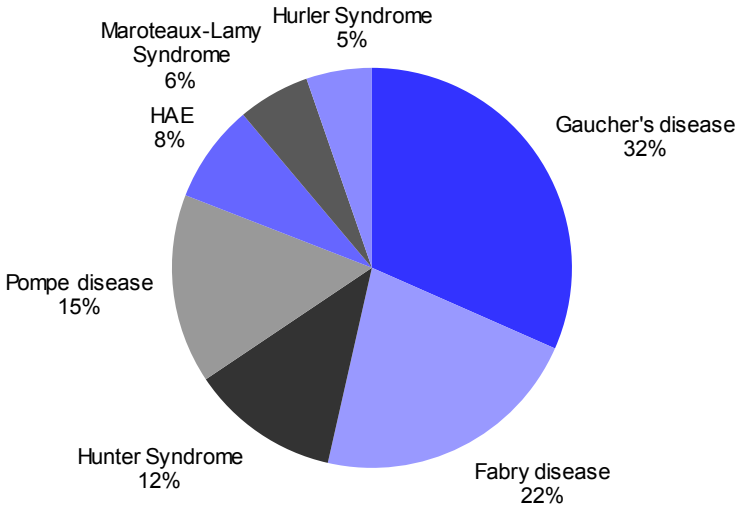
Figure 324: Orphan genetic diseases

Indication	Disease overview	Available therapies (manufacturer)
Gaucher's disease	Rare inherited disorder (but the most common of the lysosomal storage disorders), affecting c.10,000 people worldwide. Individuals lack the glucocerebrosidase (or beta-glucosidase) enzyme. This leads to lipid accumulation in organs (e.g., spleen), resulting in anaemia and osteoporosis. Type I disease (mainly seen in Askenazi Jews) is the most common and sufferers can live to adulthood. Type II (infantile) usually leads to death by the age of 2. Type III (neuropathic) is progressive and patients can live to teens or adulthood.	Cerezyme (Sanofi) VPRIV (Shire) Zavesca (Actelion) Elelyso (Protalix/Pfizer)
Fabry disease	Rare inherited disorder, affecting an estimated c.10,000 people worldwide. Individuals lack alpha-galactosidase A enzyme and cannot break down fatty substances that then build up in the organs (e.g., kidneys). This in turn leads to kidney failure, heart problems and stroke.	Fabrazyme (Sanofi) Replagal (Shire)
Hunter Syndrome	Rare inherited disorder, also known as mucopolysaccharidosis II, affecting c.2,000 (mainly males) worldwide (c.500 in US). Individuals lack iduronate-2-sulfatase enzyme and cannot break down glycosaminoglycans (GAGs), leading to distinct facial features (enlarged forehead) and breathing and walking difficulties that worsen with time.	Elaprase (Shire)
Pompe disease	Rare inherited lysosomal disorder, affecting c.9,000 worldwide, caused by accumulation of glycogen in the lysosomes. This arises due to a deficiency of alpha-glucosidase. Glycogen build-up damages muscles and the nervous system, leading to progressive weakening of muscles across the body. The disease is divided into two main categories: infantile onset (seen shortly after birth and manifested as major enlargement of the heart) and late onset (seen in juveniles or adults, with no obvious heart enlargement). Infantile onset disease is usually fatal within two years. Adult onset disease is usually life-limiting, but a small number of patients survive without major impairment to their lives.	Myozyme (Sanofi) Lumizyme (Sanofi)
Hereditary angioedema (HAE)	Rare inherited disorder, affecting between 25,000-30,000 individuals in the US, EU and Japan (prevalence 1:30,000). Individuals have a deficiency of C1 esterase inhibitor enzyme. This leads to attacks (~200,000 pa) of swelling, involving the face, limbs, etc., and can be life threatening as a result of potential asphyxiation when the swelling affects the throat.	Cinryze (Viropharma) Kalbitor (Dyax) Firazyr (Shire)
Metachromatic leukodystrophy (MLD)	Rare genetic lysosomal storage disorder which results from a deficiency of arylsulfatase-A (ASA). This in turn causes the build-up of sulfatides and destruction of the myelin sheaths around nerve fibres. MLD usually presents in children.	
Sanfilippo syndrome	Also known as mucopolysaccharidosis IIIA (MPS-III), this is a rare inherited lysosomal-storage disorder caused by a deficiency of heparan-N-sulfatase. It affects just under 2:100,000 births and manifests mainly in infants. Accumulation of heparan sulfate in various organs in Sanfilippo patients leads to neurodegeneration and typically results in death by the late teens or early twenties.	
Globoid cell leukodystrophy (GLD, aka Krabbe)	Rare inherited lysosomal disorder occurs in about 1:100,000 births (with a reportedly higher prevalence in certain Arab communities in Israel and in Scandinavia) and is mainly seen in infants. It is a neurodegenerative disease in which galactosylcerebrosidase deficiency leads to degradation of the myelin sheath of nerve fibres and deterioration of mental and motor function.	

Source: Company data, Deutsche Bank

The most lucrative ERT diseases/syndromes are Gaucher, Fabry, Hunter and Pompe, which together constitute over 80% of the market by sales value.

Figure 325: Orphan genetic disease market (2011 sales)



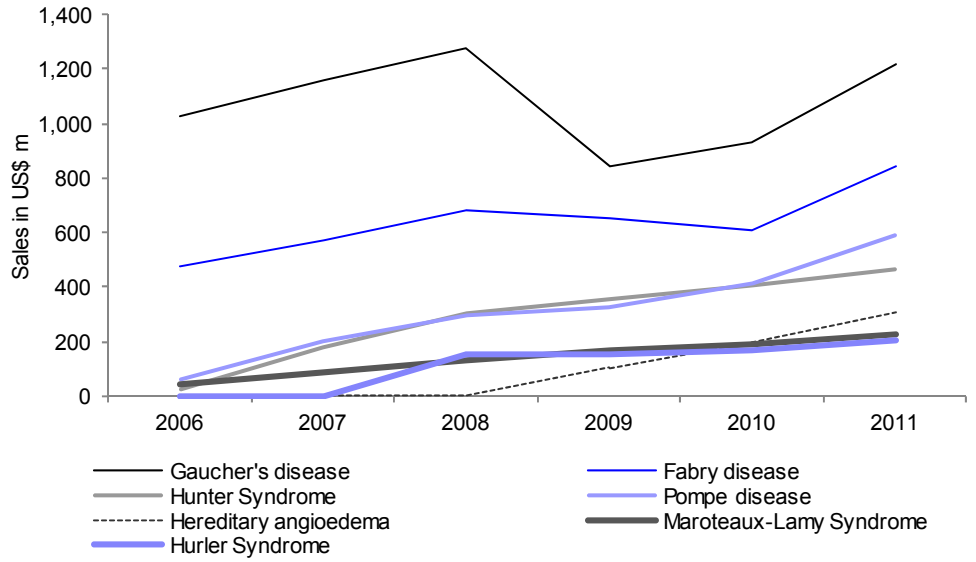
Source: Deutsche Bank, EvaluatePharma

Pipeline products

The leading players continue to research new ERTs, eg, Shire has early-stage products under evaluation for Sanfillipo syndrome and metachromatic leukodystrophy (MLD) as well as a novel drug delivery program (intrathecal injection, via a surgically-installed port) for CNS symptoms of Hunter disease. The most high profile rare disease pipeline product, however, is Sanofi's eliglustat, the first potential oral treatment for Gaucher disease (which could obviously offer increased convenience over injectable ERTs). Data from the Phase III study is expected to report 1H 2013 which Sanofi hopes will demonstrate eliglustat's efficacy and non-inferiority to Cerezyme. Data from the Phase II study met its primary composite endpoint of a clinical meaningful response in at least two of three endpoints – improvements in spleen size, hemoglobin and platelet levels. The newest entrant into rare diseases, GlaxoSmithKline, has R&D programs underway in Fabry disease and Duchenne Muscular Dystrophy (DMD) amongst others.

Sales

Figure 326: Sales of enzyme replacement therapies



Source: Deutsche Bank, EvaluatePharma

Figure 327: Sales of enzyme replacement therapies ($ m)

	2006	2007	2008	2009	2010	2011
Gaucher's disease	1,027	1,163	1,276	845	929	1,219
Fabry disease	477	572	681	650	612	847
Hunter Syndrome	24	182	305	353	404	465
Pompe disease	59	201	296	325	412	591
Hereditary angioedema	0	0	1	103	197	307
Maroteaux-Lamy Syndrome	47	86	133	169	193	225
Hurler Syndrome	0	0	152	155	167	205

Source: Deutsche Bank, EvaluatePharma

Appendix

Abbreviated New Drug Application – The regulatory process whereby a generic manufacturer wishing to produce a copy of a patented drug applies to have early physical, chemical and toxicological data and later clinically-derived safety and efficacy data for the original product taken "as read", thereby needing only to prove that its product is chemically the same as the original and is bioequivalent (behaves identically in the patient).

Absorption – As part of the ADMET acronym for drug testing is how and to what degree **animals**/animal tissues incorporate a particular chemical compound in pre-clinical testing.

ACE Inhibitors - A class of compounds that block the action of Angiotensin Converting Enzyme thereby inhibiting the production of Angiotensin II, a potent blood vessel constrictor (vasoconstrictor). ACE inhibitors are often used as treatments for hypertension and congestive heart failure.

Acetylcholine – A chemical in the body which acts as a neurotransmitter, thereby propagating nerve impulses and causing cardiac inhibition, gastrointestinal peristalsis and other parasympathetic effects.

Acetylcholinesterase – An enzyme in the central nervous system which acts specifically to breakdown the neurotransmitter, acetylcholine.

Active Control – In a clinical trial when the drug under investigation is compared with an already tested, usually approved product rather than a non-active placebo (sugar tablet).

ADMET – An acronym used in drug testing standing for the absorption, distribution, metabolism, excretion and toxicology analyses that are undertaken in animals/animal tissues in order to characterise a pre-clinical developmental compound.

Advisory Committee – One of the consulting panels of the Food and Drug Administration in the US, which often consider the merits of new products before marketing approval. Consisting of expert scientists and physicians, these committees make recommendations on approvals and/or particular courses of action in therapeutic areas. Although not bound by Advisory Committee recommendations, the FDA usually follows their advice.

Agonist – A substance that has an affinity for a particular receptor and which interacts with it to initiate a response.

Aldosterone – A steroid hormone involved in the kidney's regulation of sodium (for which it facilitates re-absorption by the body in preference to potassium).

Allergen – A substance foreign to the body that elicits an immune response, also known as an allergic reaction.

Allergic Rhinitis – Inflammation of the nasal mucous membranes associated with an allergen, often plant pollens in hay fever.

Amino Acid – Organic acids in which one of the terminal hydrogen atoms has been replaced with NH2. The twenty amino acids constitute the building blocks of proteins.

ANDA – See Abbreviated New Drug Application

Angina Pectoris – An acute severe chest pain, often radiating down the left arm, due to ischaemia (poor blood flow) of the heart muscle, usually caused by coronary disease.

Angioplasty – A procedure to open narrowed arteries, usually via the introduction of a balloon tip catheter, which is then inflated to dilate the narrowed portion of the vessel.

Angiotensins – Compounds with profound blood vessel constricting (vasoconstrictive) activity, which are produced by the enzymatic action of renin on angiotensinogen.

Angiotensin I – A compound formed from angiotensinogen in an enzymatic reaction facilitated by renin. Further enzymatic action (via angiotensin-converting enzyme) forms angiotensin II, which produces constriction of the blood vessels.

Angiotensin II – A compound formed from Angiotensin I in a reaction mediated by angiotensin-converting enzyme. Angiotensin II significantly increases blood vessel constriction and therefore blood pressure. It is also the most powerful stimulus for the production and release of aldosterone.

Angiotensin Converting Enzyme – A compound that mediates the conversion of Angiotensin I, a relatively inert substance in the body, into Angiotensin II, a potent blood pressure-raising agent.

Angiotensin II Receptor Blockers – A class of compounds that interfere with the action of Angiotensin II, a potent blood pressure-raising agent, thereby producing a fall in blood pressure. Often used in the treatment of hypertension.

Angiotensinogen – A compound produced by the liver that is converted to angiotensin I by renin. It is involved in the renin-angiotensin system that regulates blood pressure levels.

Antagonist – A substance that has an affinity for a particular receptor and inhibits another agent from eliciting a response from that receptor.

Anti-aggregants – Drugs used to prevent the clumping of blood platelets. Such products have proved useful in the treatment of a number of cardiovascular conditions.

Antibody – Proteins produced by the body, which make up an important part of the immune system. They specifically target and destroy foreign proteins (antigens).

Antigen - A protein that is foreign to the body and which provokes the production of neutralising antibodies by the immune system. These antibodies specifically target and destroy the antigen.

Antisense Technology – The use of single nucleotide chains which act as therapies by matching up and binding to specific mRNA molecules, thereby blocking protein synthesis.

Apoptosis – The programmed cell death inherent to all normal cells at the appropriate stage of their life cycle. An apoptosis malfunction where it fails to occur is possibly involved in the undifferentiated cell division seen in cancer tissue proliferation.

Apolipoprotein – Is the protein component of lipid and lipoprotein complexes. These are a normal component of High, Low and Very Low Density Lipoproteins in Man.

Arterial – Pertaining to vessels carrying blood away from the heart.

As Treated – In a clinical trial, this analysis includes only those patients completing treatment. Those dropping out of the study are not included. This is not as robust an analysis as an "Intent To Treat" analysis, where all patients registered in the trial are included in the analysis.

Atherogenesis – The formation of atheroma or lipid (fatty) deposits, usually in artery walls. These are important in the pathogenesis (development) of arteriosclerosis.

Atherogenic – Having the ability to initiate, to increase or accelerate the process of atherogenesis.

Atheroma – Lipid (fatty) deposits in the walls of the arteries, producing a yellow swelling on the inner endothelial surface, characteristic of atherosclerosis.

Atherosclerosis – A nodular hardening of the arteries associated with the buildup of fatty deposits, the formation of fibrous tissue and calcification.

Baroreceptor - Receptors located in the vascular system and the heart which are sensitive to wall distension due to increased pressure. They form part of the reflex mechanism that controls blood pressure.

Base Pairs – Couplings formed by the specific bonding of the nitrogenous bases adenine, thymine, cytosine and guanine, between complementary strands of DNA. Adenine binds with thymine and cytosine with guanine.

b.i.d. (or b.d.) – Instructions written on a prescription, indicating the medication should be taken twice-daily.

Beta-Adrenergic Receptors – Cell surface proteins that bind to transmitters of the autonomic nervous system such as norepinephrine. Stimulus leads to the classic 'fight or flight' response with an increase in heart rate and blood pressure.

Beta cells – Cells in the pancreas responsible for the production and secretion of insulin.

Beta-Blockers – A group of compounds that block the stimulus of beta-adrenergic receptors. Actions include a slowing of the force and rate of heart contractions. Often used in the treatment of hypertension and anxiety.

Biomarker - A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.

Biotechnology – The use of cell chemistry to produce therapeutically useful proteins. Biotechnology seeks to industrialise and manipulate chemical reactions at the cellular level to produce significant quantities of often complex molecules.

Black Box Warning – In the US, a product can be launched or eventually issued with this severe warning that is included with its prescribing information. Such a warning usually refers to potentially life-threatening adverse effects.

Blockbuster – A product with annual sales of $1bn or more may also be termed a 'blockbuster'.

Blood pressure – The pressure within vessels of the body which blood. Usually measured in millimetres of Mercury (mmHg) and expressed as two components - systolic, which refers to the pressure in blood vessels generated during contraction of the heart and diastolic, which refers to the pressure in the same vessels when the heart is relaxed. Normal readings are around 120mmHg for systolic pressure and 80mmHg for diastolic pressure.

Body Mass Index – A measure of obesity; also used as an indicator of likely complications due to excess weight. This is calculated as an individual's weight in kilograms divided by the square of his/her height in metres.

Bronchospasm – The tightening of the smooth muscle surrounding the ariways of the lungs associated with an asthma attack.

Calcium Channel Blockers – A class of compounds that act by inhibition of the passage of Calcium ions into muscle cells, which causes relaxation of the muscle. They are often used as treatments for hypertension and angina.

Cardiac Output – A measure of the rate of blood pumped out of the heart, usually calculated as the heart rate multiplied by the volume of contraction.

Cascade – Pertaining to a sequence of chemical reactions within the body.

Catabolism – The break down of complex chemical compounds into simpler ones, often with the release of energy.

Catheter – A tubular instrument designed to allow passage of fluid from or into a body cavity. For example, in angioplasty, a balloon tip catheter is fitted with an inflatable tip, which can be used to facilitate passage of the tube through the blood vessel, to take haemodynamic (blood flow-related) measurements or to open a partially blocked blood vessel (angioplasty).

Cells – The smallest unit of living structure capable of independent existence, composed of a membrane-enclosed mass of protoplasm and containing a nucleus.

Central Nervous System – That portion of the nervous system comprising the brain and spinal column.

Cerebral Embolism – An obstruction of the blood vessels supplying the brain, most often composed of a detached blood clot from a distant site.

Chemotaxins – Chemical substances that mediate the movement of cells or organisms.

Chiral – Denoting a chemical that can exist in a number of forms. A term usually used in relation to the different isomers of a particular compound. Isomers have identical chemical compositions but have atoms in differing positions within the molecule, thus

giving rise to different shapes and potentially leading to differing chemical and physical properties.

CHMP – See Committee for Medicinal Products for Human Use

Cholesterol – The most abundant steroid present in animal tissues, especially in bile and gall stones, and also present in food. It is important in the pathogenesis of atheroma formation in the arteries.

Chromosome – Packages of genetic information, in the form of DNA, located in the nucleus of cells. In humans 23 pairs of chromosomes contain an estimated 100,000 genes which code for specific proteins.

Clone – An individual organism or group of organisms derived from a single organism or cell and therefore having identical genetic make-up.

Codon – A triplet of nucleotides made from adenine, thymine, cytosine and guanine, which codes specifically for one of the twenty amino acids. The number and sequence of codons along a gene sequence determine the structure of the protein made by that gene.

Combinatorial Chemistry – The systematic, usually automated, synthesis of large numbers of similar, but distinct, chemical compounds in preparation for drug activity screening.

Committee for Medicinal Products for Human Use – An advisory committee to the European Medicines Evaluation Agency (EMA), which assesses New Drug Applications.

Contractility – The ability of a substance, especially of muscle, of shortening, or becoming reduced in size, resulting in increased tension.

Control Regions – Sequences within the non-protein coding portion of the DNA, which act to regulate gene expression and therefore protein synthesis.

Corticosteroids – Steroids produced by the adrenal gland in the body.

Crossover – In a clinical trial, when patient groups alternate between the various treatment arms and/or placebo during the course of the study.

Cytokines – Non-antibody proteins within the body which are released by certain cells in response to specific antigens and which mediate the immune response.

Cytoplasm – The main constituent of a cell comprised of gel-like living matter, containing various cellular structures and the nucleus.

Deep-Vein Thrombosis – A condition relating to the formation of blood clots, often in blood vessels of the lower limbs, following surgery or extended periods of immobilisation. These blood clots may potentially block blood vessels locally or can detach and cause blockage elsewhere, for example in the lungs (pulmonary embolism) or brain (cerebral embolism).

Diabetes – A metabolic disease in which carbohydrate utilisation is reduced and that of lipid and protein enhanced. It is caused by an absolute or relative deficiency of insulin

and manifests as raised glucose levels in the blood. Long term complications include damage to nerves, the kidney and eyes.

Diastole – The resting or relaxation phase of the beating heart. The pressure in blood vessels during relaxation forms part of the measurement of blood pressure (see also systole, and hypertension).

Distribution – As part of the ADMET acronym for drug testing is the distribution of a particular chemical throughout animals/animal tissues in pre-clinical testing.

Diuresis – Denotes the excretion of unusually large volumes of urine.

Diuretic – An agent that promotes the production of urine.

DNA – Deoxyribonucleic Acid. A strand of molecules containing genetic instructions comprising of linked and repeating sub-units called nucleotides, based on the nitrogenous bases adenine (A), thymine (T), cytosine (C) or guanine (G). Each of these bases pairs with another on a complementary strand of DNA (A with T and C with G) to form a double helix.

Double Blind – In a clinical trial when neither the patient nor the investigating physician is aware what has been administered, be it active treatment or placebo.

Drug Label – The prescribing instructions and other product information agreed with the Food and Drug Administration, which is routinely included in the packaging of a drug product.

Embolism – An obstruction of vessels, usually blood vessels, most often composed of detached blood clot from a distant site, a mass of bacteria or other foreign body.

EMA – See European Medicines Agency

Enantiomer – One of a pair of molecules that are mirror images of each other.

Endothelial cells – Flat cells that typically line the walls of blood cells and the heart. The lining of a layer of such cells is known as endothelium.

Enzyme – A protein secreted by cells, which acts as a promoter or catalyst of chemical reactions in the body while remaining unchanged by the reaction itself.

Eosinophils – A form of white blood cell which play a role in combating parasites. It is also involved in the mediation of allergic reactions and asthma.

Epilepsy – A brain disorder in which a person has repeated seizures (fits) over time.

Essential Hypertension – Blood pressure that is raised above normal but with no discernible cause. Also known as idiopathic hypertension.

European Medicines Agency – The European Union's drug regulatory agency which oversees all aspects of pharmaceutical regulation, from clinical trials and registration, through to manufacturing standards and promotional claims.

Excretion – As part of the ADMET acronym for drug testing is the method by which animals/animal tissues rids itself of a particular chemical compound and its breakdown products in pre-clinical testing.

Exogenous – A substance that is produced outside an organism.

FDA – See Food & Drug Administration

Fee-For-Service – The most flexible of Managed Care plans where individuals may select their physician and receive the treatment considered most suitable by that doctor.

FEV1 – Forced Expiratory Volume of air expelled from the lungs in one second. A frequently used test of the severity and resolution of an asthma attack.

Fibrin – An elastic filamentous protein derived from fibrinogen via the action of thrombin. It is a component of blood clots.

Fibrinolysis – The breakdown of fibrin by a chemical reaction known as hydrolysis. In therapeutic terms, this is carried out with products known as fibrinolytics.

Food & Drug Administration – The US regulatory agency which oversees all aspects of pharmaceutical regulation, from clinical trials and registration, through to manufacturing standards and promotional claims.

Formulary – A list of pharmaceuticals which has been approved for reimbursement by a particular institution.

Gastrin – A hormone secreted in the mammalian stomach which stimulates the secretion of hydrochloric acid by the parietal cells of the gastric glands.

Gene – A specific sequence of nucleotides, or DNA sub-units, that direct protein synthesis.

Gene Expression – Refers to whether a gene is 'turned on' or activated to direct protein synthesis. Specific control regions within junk DNA regulate gene expression.

Generic – The basic chemical constituent of a pharmaceutical product.

Genome – The blueprint of genetic information of an organism often referred to in humans as the "book of life." The Human Genome, which was finally sequenced in June 2000, comprises some 3.1bn base pairs of information, only 10% of which are thought to code for proteins, arranged on 23 pairs of chromosomes.

Genomics – The study of all aspects of the Genome, the blueprint of genetic information, particularly its structure and function, as it relates to humans.

Genotype – The genetic constitution of an individual, sometimes used with respect to the make-up of a group of individuals with similar characteristics as determined by one gene.

GERD – Gastro-Esophageal Reflux Disease, a condition in which acid is regurgitated from the stomach into the esophagus causing heartburn pain and in more severe

chronic cases, tissue erosion. Acid secretion suppressants such as H2-blockers and proton pump inhibitors are used to treat the condition.

Glitazones – A class of chemicals also known as the thiazolidinediones, which are sensitisers of body tissue to insulin and are, therefore, used as treatments for diabetes. Examples include Actos (Takeda/Lilly), Avandia (GlaxoSmithKline) and the now withdrawn Rezulin (Pfizer).

Glucagon – A hormone involved in glucose metabolism. It promotes the elevation of blood glucose levels by the breakdown of glycogen in the liver.

Glucocorticoids – A steroid-like compound capable of significantly influencing intermediary metabolism and of exerting a clinically useful anti-inflammatory effect.

Glucogenic – Increases the production of glucose in the body.

Glycosylated haemoglobin – Any one of the four haemoglobin A fractions (AIa1, AIa2, AIb and AIc) which has glucose or related monosaccharides bound to it. Concentrations are raised in the red blood cells of patients with Diabetes Mellitus, and can be used as a retrospective measure of glucose control over time in such patients.

H2 Antagonists – A class of compounds that inhibit the action of histamine receptors in the stomach, reducing gastric acid secretions. As such, they are useful in the treatment of GERD and ulcer disease.

Haemoglobin – A protein found in red blood cells responsible for the oxygen carrying capacity of the blood.

Haemodynamic – Pertaining to the movement of blood.

Haemorrhagic stroke – A condition in which there is bleeding in the tissues of the brain.

Health Maintenance Organisation – Part of the managed care system, these groups administer the drug benefit of individuals, usually on behalf of their employer. The pooling of large numbers of people in HMO schemes allows bulk purchasing and the negotiation of discounts. These organisations range from relatively inflexible Staff Model HMOs, which employ physicians and use strict formularies to control drug availability, through to Group or Network HMOs where the physician is contracted to one, or a number of HMOs, respectively. Inevitably, less influence can be exerted on physicians' prescribing decisions in these more loosely structured entities.

HDL-cholesterol – High-density lipoprotein cholesterol is one of a number of lipid-protein complexes present in the body. Also colloquially known as "good" cholesterol because of the beneficial effect it has on the evolution of cardiovascular disease.

High Throughput Screening – The systematic, usually automated rapid screening of compounds through a wide range of assays to determine their biological activity.

Histamine – A compound that is a powerful stimulant of gastric secretions and plays an important role in allergic reactions. It facilitates smooth muscle constriction and is a vasodilator of both capillaries and arterioles. Its inhibition is therefore useful in the treatment of a number of conditions including GERD, ulcer disease, allergy and asthma.

HMG Co-A reductase – 3-hydroxy-3-methylglutaryl coenzyme A reductase is the rate-limiting enzyme in the intracellular synthesis of cholesterol. Its action is inhibited by the statins which are the most frequently used compounds for cholesterol reduction.

HMO – see Health Maintenance Organisation.

Hormone – A chemical substance formed in one organ or part of the body which then exerts its effect elsewhere within the body.

Hydrolysis – A chemical process whereby a compound is cleaved into two or more simpler compounds with the uptake of water. It is effected by the action of acids, alkalis, or enzymes.

Hyperglycaemia – An excess of glucose in the circulating blood, especially with reference to fasting levels.

Hypertension – A condition in which blood pressure is raised above the normal range as measured in millimetres of Mercury (mmHg). Blood pressure is expressed in two components - Systolic, which relates to the pressure in blood vessels generated during contraction of the heart and diastolic, which relates to the pressure in those vessels when the heart is relaxed. Treatment to reduce hypertension is usually considered appropriate once systolic pressure exceeds 140mmHg and/or diastolic pressure exceeds 90mmHg.

Hypoglycaemia – An abnormal depletion of circulating blood glucose levels sometimes caused by an overdose of diabetes treatments such as insulin.

Hypotension – A blood pressure that is lower than the normal range as measured in millimetres of Mercury (mmHg). Blood pressure is expressed in two components - Systolic, which relates to the pressure in blood vessels generated during contraction of the heart and diastolic, which relates to the pressure in the same vessels when the heart is relaxed. Optimal blood pressure is regarded as 120mmHg diastolic and 80mmHg systolic.

Incidence – The number of new cases of a disease in a defined population over a specific period of time.

IND – see Investigational New Drug.

Independent Physician Association – A loosely based collection of physicians in an organisation that is part of the Managed Care system. The range of suggested formularies they employ allows negotiated discounts for bulk drug purchases to be obtained but in reality IPAs exert little influence on physicians' prescribing habits.

Inflammation – The term for the collective changes that occur in tissues in response to injury and which eventually lead to healing. These changes principally, but not always, involve redness, warmth, swelling and pain.

Inotrope – A compound that affects the contractility of muscular tissue. Usually relates to the use of positive inotropes in heart failure.

In silico – Pertaining to experiments or reactions occurring on a silicon chip. Relates particularly to advances in experimental biology.

Insulin – A peptide hormone secreted by beta cells in the pancreas that promotes glucose utilisation, protein synthesis and neutral lipid storage. It is used in an injectable formulation for the treatment of diabetes mellitus.

Intent to Treat – In a clinical trial this analysis includes all patients originally registered, even if they subsequently withdrew from the study. This is a more robust analysis than "as treated" where only those patients completing treatment are included.

Intracellular – Occurring within the cell.

Investigational New Drug (IND) – A drug candidate for which the sponsor company has permission from the regulatory authorities, usually the US Food and Drug Administration, to test a particular compound in clinical trials.

In vitro – Pertaining to experiments or reactions occurring in the artificial environment that is the laboratory test-tube. Literally meaning "in glass."

In vivo – Pertaining to experiments or reactions occurring within a living organism.

Ions – An atom or group of atoms carrying an electric charge.

IPA – See Independent Physician Association.

Ischaemia – A reduction in blood flow to tissues usually as a result of blood vessel blockage.

Ischaemic Stroke – A condition in which there is blockage of a blood vessel supplying a portion of the brain, leading to brain tissue damage.

Isomers – The different forms in which certain compounds can exist. Isomers have identical chemical compositions but have atoms in differing positions within the molecule thus conferring them with variable shapes potentially leading to differing chemical and physical properties.

Junk DNA – Regions of DNA strands that have no known coding properties for protein synthesis. Of the 3.1bn base pairs of genetic information only 10% is thought actively to code for protein synthesis. Within the remainder, sequences of DNA act as control regions to regulate gene expression.

LDL-Cholesterol – Low-density lipoprotein cholesterol is one of a number of lipid-protein complexes present in the body. Also colloquially known as "bad" cholesterol because of the detrimental effect it has on the evolution of cardiovascular disease.

Leukotrienes – Products of Arachidonic acid metabolism thought to be involved as mediators of inflammation and with a role in the allergic response.

Lipids – Usually referring to fat or substances derived from fat.

Lipoproteins – Compounds or complexes in the body which contain both lipids and proteins.

Lumen – The space forming the interior of a tubular structure such as a blood vessel or intestine.

Lymphocyte – A form of white blood cell originating from lymphatic tissue (e.g. lymph nodes, spleen. Thymus, tonsils etc).

Macrophages – Large, long-lived cells widely distributed throughout the body, which are actively involved in the body's defence against disease. They actively engulf and destroy invading bacterial and inert substances and are involved in the production of antibodies and cell-mediated immune response.

Managed Care – A concept employed in the US, which involves appointing specific providers to the task of managing actively the provision of healthcare for a group of individuals. For example, this involves Health Maintenance Organisations, which administer the drug benefit of individuals, usually on behalf of their employer. The pooling of large numbers of people in HMO schemes allows bulk purchasing and the negotiation of discounts. These organisations range from relatively inflexible Staff Model HMOs, which employ physicians and use strict formularies to control drug availability, through to Group or Network HMOs where the physician is contracted to one, or a number of HMOs, respectively. Inevitably, less influence can be exerted on physicians' prescribing decisions in these more loosely structured entities.

Markers – Surrogate endpoints, the measurement of which is often used in clinical trials to demonstrate a response to treatment. This may involve measurements such as copies of a virus (viral load in HIV trials) or proteins indicative of tumour activity in cancer trials.

Mast Cells – A connective tissue cell that is believed to contain substances, which are mediators of the allergic response such as histamine.

Medicaid – A US scheme funded by State and Federal government designed to provide the cost of hospitalisation, doctors' visits and prescription drugs for individuals with low incomes.

Medicare – The US nationwide federally funded healthcare programme for the elderly and disabled.

Membrane – A covering or skin for cells, tissues or organs within the body.

Messenger Ribonucleic Acid – A molecule transcribed in the cell nucleus using unwound DNA as a template. It is almost the same as the original DNA with the exception that another nucleotide, uracil, takes the place of thymine. The mRNA molecule then moves out of the nucleus into the surrounding cellular fluid, or cytoplasm, where it attaches to a ribosome to be read (translated) producing a protein.

Metabolism – As part of the ADMET acronym for drug testing is the way animals/animal tissues break down a particular compound in pre-clinical testing.

Metastasis – The spread of a disease, or its local manifestations, from one part of the body to another; used to refer to the development of new cancerous growths remote from the site of the primary tumour.

MHLW – see The Ministry of Health, Labour and Welfare.

Ministry of Health, Labour and Welfare – The Japanese government's drug regulatory agency which oversees all aspects of pharmaceutical regulation, from clinical trials and registration, through to manufacturing standards and promotional claims.

Molecular Imaging – A technique used in drug development that provides information on the shape and configuration of a substance under investigation.

Monoclonal (Antibody) – A specific antibody produced from a clone or genetically identical population of hybrid cells.

Mononuclear – Having only one nucleus. Used especially in reference to blood cells.

Monosaccharides – Single molecules of sugar. The most basic form of carbohydrates.

Monotherapy – The treatment of a condition with only one product.

mRNA – see Messenger Ribonucleic Acid.

Mucosa – The mucous lining of various tubular structures within the body, consisting of epithelium, lamina propria (a layer of connective tissue) and, in the digestive tract, a layer of smooth muscle.

Mucus – A clear viscid secretion of the mucus membranes, consisting of mucin, epithelial cells, leukocytes and various inorganic salts suspended in water.

Myocardial infarction – Heart attack, as in infarction or death of heart tissue (myocardium) brought about by a sudden loss of blood supply.

National Institute for Clinical Excellence – A UK government advisory body which considers the cost effectiveness of new products.

NDA – See New Drug Application.

Neurotransmitter – Any specific substance released by a nerve cell on stimulation, which crosses the synapse (nerve gap) which divides nerve cells, to stimulate or inhibit the post-synaptic nerve cell.

New Chemical Entity – As the name implies, a newly synthesised compound for which a sponsor company will likely undertake drug development.

New Drug Application (NDA) – The filing made to the regulatory authorities, usually the Food and Drug Administration, by a drug sponsor for the approval of a product once clinical testing has been completed.

NICE – See National Institute for Clinical Excellence.

Nitrogenous Bases – Adenine, thymine, cytosine and guanine are the four molecules that bind following specific rules (adenine with thymine, cytosine with guanine) and are the basic building blocks of DNA.

NSAIDs – Non-steroidal anti-Inflammatory drugs. A group of drugs used for the treatment of pain and inflammation associated with a number of conditions such as arthritis.

Nucleotides – Linked and repeating sub-units of DNA strands which are based on the four nitrogenous bases adenine, thymine, cytosine and guanine.

Nucleus – The central, typically rounded structure of the plant or animal cell containing the genetic information.

Obese – An overweight person with a calculated body mass index (BMI) of 30 or higher. BMI is an indicator of likely complications due to excess weight and is calculated as an individual's weight in kilograms divided by the square of his/her height in metres.

Oedema – Swelling caused by the accumulation of fluid in the tissues.

Oesophagus – The portion of the digestive canal between the throat region, or pharynx and the stomach.

Open Trial – A clinical trial where both the patient and investigating physician are aware what has been administered, be it active treatment or placebo.

Orange Book – The US Food and Drug Administration's list of patents recognised on approved branded products.

Orphan Drug – A drug recognised by the regulatory authorities (different conditions apply in different geographies) as being useful for a relatively rare condition affecting only a limited number of patients. Orphan Drug status affords certain assistance to the drug sponsor (R&D grants, favourable tax treatment, etc) and a period of market exclusivity for the product.

Overweight – A person with a calculated Body Mass Index (BMI) in a range of 25 to 29.9. BMI is an indicator of likely complications due to excess weight and is calculated as an individual's weight in kilograms divided by the square of his/her height in metres.

Oxidise – A reaction in which a compound is combined with oxygen or loses electrons.

P-value – A statistical term measuring whether a trial outcome is statistically significant. In clinical trials, a p-value of less than 0.05 is deemed to be statistically significant.

Parasite – An organism that lives in or on another and derives nourishment from it.

Patent – Legally granted ownership protection, usually 20 years, for scientific innovation, given to a company that has discovered a new molecule or novel scientific process.

PDUFA – Prescription drug user fee (see 'user fee'). Often used in reference to a date for which to expect the FDA to make a decision on a new drug application.

Pepsin – The principal digestive enzyme of gastric juice, formed from pepsinogen.

Pepsinogen – An inactive enzyme formed and secreted by the chief cells of the gastric mucosa which is acted upon by gastric juices and pepsin itself to form active pepsin.

Peptide – A compound comprising of two or more amino acids.

Peristalsis - A rhythmic wave of contractions and relaxation alternating along the length of the intestine or other tubular structure which propel its contents along its length.

Peroxisome proliferator-activated receptor (PPAR) agonists – A group of compounds which stimulate PPA receptors. They are used or under investigation for the treatment of diabetes.

Personalised medicine – Tailoring of medical treatment to the individual characteristics of each patient, to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment.

Pharmacogenetics – The genetic basis for variation in drug response.

Pharmacogenomics – A group of related technologies concerned with understanding the genetic basis of a drug response.

Pharmacokinetics – The movement of drugs within biological systems as affected by their uptake and distribution through the body, binding to receptors and tissues, elimination from the body and the effect the body has on the drug.

Pharmacology – The science concerned with drugs, their sources, appearance, chemistry, actions and uses.

Pharmacopoeia – A collection of drug product descriptions, or monographs, which depict their characteristics and the properties and standards for the strength and purity of those compounds.

PhRMA – Pharmaceutical Research & Manufacturers of America is the leading trade association of the Ethical Pharmaceutical industry in the US.

Phospholipids – Lipids (fatty substances) containing phosphorus.

Placebo – The non-active reference material (often referred to as a 'sugar pill') used in clinical trials designed to determine the relative efficacy of a drug candidate.

Plasma – The liquid portion of blood.

Plasmin – An enzyme (aka. Fibrinolysin), that converts insoluble fibrin into soluble products. It is found in plasma as plasminogen and is activated to plasmin.

Platelet – An irregularly shaped structure found in the peripheral blood containing granules and cytoplasm but with no definite nucleus, which is involved in the blood clotting process.

Point of Service – A healthcare plan under which individuals can consult one of a number of physicians recommended by the plan manager. This physician will then be responsible for the basic healthcare needs of the patient but can refer to a specialist should the need arise. However, referral can lead to further out-of-pocket expense for the patient.

Polymorphisms – Literally "many forms" is used in the context of DNA analysis to highlight the small variations that produce diversity between individuals.

Polysaccharides – A carbohydrate containing a large number of saccharide (sugar) groups.

PPO – See Preferred Provider Organisation.

Preferred Provider Organisation – A healthcare plan under which patients can elect to consult one of a number of physicians recommended by the PPO manager. The physician provides a discount on usual fees in return for regular referrals from the PPO. Patients can consult a non-plan physician for an additional out-of-pocket expense.

Prevalence – The number of cases of a disease existing in a given population at a particular moment in time.

Primary End-Point – In a clinical trial, this is the most important pre-determined objective of the study.

Priority review – An accelerated review period for a New Drug Application within the Food and Drug Administration's user fee system. This six-month review is shorter than the standard ten-months.

Prophylactics – Drugs used to prevent a disease or a process that can lead to disease.

Proteins – Large molecules consisting of chains of amino acids. They comprise three-quarters of the dry weight of most cell matter and are involved in structures, hormones, enzymes, muscle contraction, immunological response and essential life functions.

Proteomics – The study of proteins in terms of their synthesis, structure and function.

Proton Pump – The mechanism by which Hydrogen ions are released into the stomach, thereby forming an acid environment to facilitate the digestion of food.

Protoplasm – The living matter that comprises the inside of cells, be they animal or vegetable, in which the nucleus is suspended.

Pulmonary Embolism - An obstruction of the pulmonary arteries of the lung, most often composed of detached blood clot from a distant site following an operation or immobilisation in bed.

Q.D. (from latin 'quaque die') – Referring to instructions on a prescription, meaning the medicine is to be taken once daily.

QT prolongation –A distortion of the normal conduction of electrical impulses across the heart, which manifests as an extension of the time between two points (Q and T) on an electrocardiograph. A potentially life-threatening side effect noted with a number of pharmaceuticals.

Radioisotope – A radioactive version of an element, which gradually loses its larger number of neutrons via the emission of radiation. Radioisotopes are often used in the localised treatment of tumours.

Randomised – In a clinical trial, when patients are equally likely to be assigned to the active drug versus placebo arm regardless of disease or demographic characteristics.

Rational Drug Design – The systematic design of new drug candidates using molecular modeling and a detailed knowledge of the properties of various chemical compounds.

Racemic – The name given to an optically inactive mixture of two or more separable isomers.

Receptor – A structural protein on the cell surface or within the cytoplasm of a cell that binds to a specific factor, such as a hormone, antigen or neurotransmitter.

Recombinant – A microbe, or strain, that has received chromosomal parts from different parental strains. Often used to denote the insertion of a sequence of DNA, by chemical or biological means, into the DNA of a recipient organism with the objective of producing therapeutically useful products.

Renin – An enzyme that converts angiotensinogen to angiotensin and, part of the renin-angiotensin-aldosterone system is involved in the regulation of blood pressure.

Ribosome – A structure in the cytoplasm of a cell which facilitates the reading (translation) of a strand of mRNA into a protein by the specific selection and adding together of a chain of amino acids.

Seasonal Allergic Rhinitis – An inflammation of the nasal mucous membranes associated with plant pollen as allergens. Also known as hay fever.

Secondary End-Point – In a clinical trial, these are pre-determined objectives for analysis but deemed less important than the Primary end-point.

Secretagogue – An agent that promotes secretion.

Single Blind – In a clinical trial where the physician but not the patient is aware what has been administered be it active treatment or placebo.

sNDA – See Supplementary New Drug Application.

SNPs – Single nucleotide polymorphisms are minor changes in the make up of DNA that account for the variation between individuals.

Spasmogens – A substance, usually released by the body in response to stimulus, which causes spasms in smooth muscle. In the lungs this leads to contraction of the airways, the so-called asthma attack.

Statins – A colloquial collective name for HMG Co-enzyme A reductase inhibitors, which are frequently used to reduce cholesterol levels.

Supplementary New Drug Application – The regulatory process where an application is made for a new indication or formulation for use in the USA. It is filed with the Food and Drug Administration.

Synapse – The functional membrane to membrane contact of a nerve cell with another nerve cell, an effector (muscle or gland) cell, or a sensory receptor cell. The synapse subserves the transmission of nerve impulses, usually via the release of a neurotransmitter into the synaptic cleft (or gap) which then exerts an effect on cells on the other side of the cleft.

Systemic – Refers to an action within the body. Usually used in the context of the action of a pharmaceutical.

Systole – The contracting phase of the beating heart. The pressure in blood vessels produced by such contraction forms part of the measurement of blood pressure (see also diastole and hypertension).

T-cells – A long-lived cell of the immune system also known as a T lymphocyte, which is responsible for the cell mediated immunity.

Thrombosis – The formation or presence of a blood clot (thrombus) within blood vessels, which may cause infarction (death) of the tissues supplied by that vessel.

t.i.d. – Refers to instructions written on a prescription, meaning the medicine is to be three times a day.

Total Peripheral Resistance – The resistance to the passage of blood around the body, caused primarily by the small blood vessels of the vascular system.

Toxicology – As part of the ADMET acronym for drug testing is the toxicity profile demonstrated in animals/animal tissues by a particular compound in pre-clinical testing.

Toxin – A substance that is poisonous to the organism.

Transcription – The process whereby mRNA is produced by the binding of nucleotides in the nucleus of a cell using unwound DNA as a template. The mRNA produced is almost the same as the original DNA with the exception that that a fifth nucleotide, uracil, takes the place of thymine.

Transgenic – An animal that has been produced from a cell cloned after genetic alteration to carry genes, usually human, that will allow the production of therapeutically useful (human) proteins

Translation – The process whereby the mRNA molecule produced by the binding of nucleotides during transcription moves out of the nucleus of the cell into the surrounding cellular fluid, or cytoplasm. There it attaches to a ribosome and is read, or translated into a sequence of amino acids, which are joined together to form a protein.

Unblinded Trial – A clinical trial where both the patient and investigating physician are aware what has been administered, be it active treatment or placebo.

User Fee (Deadline) – A sum of money which a company sponsoring a New Drug Application in the US pays to the Food and Drug Administration for review of the product. In return the FDA agrees to render a decision on the application within ten-months for a standard review and within six-months (priority review) for a product which represents a significant advance on existing therapies.

Vasculature – The vascular (blood vessel) network of an organ.

Vasoconstriction – The narrowing of the blood vessels, usually leading to an increase in blood pressure.

Vasodilation – The relaxation of blood vessels, usually leading to a decrease in blood pressure or an increase in blood flow.

Vasopressor – An agent producing vasoconstriction (contraction of the blood vessels) and an increase in blood pressure, usually understood to be systemic arterial pressure, unless otherwise specified.

Ventricles – The lower chamber of the heart responsible for pumping blood out of the heart to the rest of the body.

VLDL-cholesterol – Very Low-density lipoprotein cholesterol is one of a number of lipid-protein complexes present in the body. It has a detrimental effect on the evolution of cardiovascular disease although not as pronounced as LDL-cholesterol.

The authors of this report wish to acknowledge the contribution made by Swati Saxena, employee of Irevna, a division of CRISIL Limited, a third-party provider to Deutsche Bank of offshore research support services.

Appendix 1

Important Disclosures

Additional information available upon request

For disclosures pertaining to recommendations or estimates made on securities other than the primary subject of this research, please see the most recently published company report or visit our global disclosure look-up page on our website at http://gm.db.com/ger/disclosure/DisclosureDirectory.eqsr

Analyst Certification

The views expressed in this report accurately reflect the personal views of the undersigned lead analyst about the subject issuers and the securities of those issuers. In addition, the undersigned lead analyst has not and will not receive any compensation for providing a specific recommendation or view in this report. Jeremy Lai/Tim Race/Mark Clark/Richard Parkes/Holger Blum

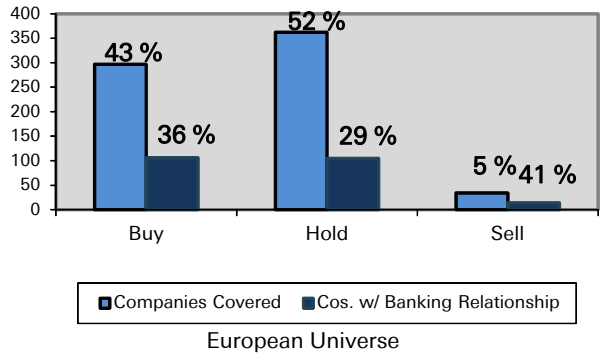
Equity rating key

Buy: Based on a current 12- month view of total share-holder return (TSR = percentage change in share price from current price to projected target price plus pro-jected dividend yield) , we recommend that investors buy the stock.
Sell: Based on a current 12-month view of total share-holder return, we recommend that investors sell the stock
Hold: We take a neutral view on the stock 12-months out and, based on this time horizon, do not recommend either a Buy or Sell.
Notes:

1. Newly issued research recommendations and target prices always supersede previously published research.
2. Ratings definitions prior to 27 January, 2007 were:

Buy: Expected total return (including dividends) of 10% or more over a 12-month period
Hold: Expected total return (including dividends) between -10% and 10% over a 12-month period
Sell: Expected total return (including dividends) of -10% or worse over a 12-month period

Equity rating dispersion and banking relationships



European Universe

Regulatory Disclosures

1. Important Additional Conflict Disclosures

Aside from within this report, important conflict disclosures can also be found at https://gm.db.com/equities under the "Disclosures Lookup" and "Legal" tabs. Investors are strongly encouraged to review this information before investing.

2. Short-Term Trade Ideas

Deutsche Bank equity research analysts sometimes have shorter-term trade ideas (known as SOLAR ideas) that are consistent or inconsistent with Deutsche Bank's existing longer term ratings. These trade ideas can be found at the SOLAR link at http://gm.db.com.

3. Country-Specific Disclosures

Australia and New Zealand: This research, and any access to it, is intended only for "wholesale clients" within the meaning of the Australian Corporations Act and New Zealand Financial Advisors Act respectively.
Brazil: The views expressed above accurately reflect personal views of the authors about the subject company(ies) and its(their) securities, including in relation to Deutsche Bank. The compensation of the equity research analyst(s) is indirectly affected by revenues deriving from the business and financial transactions of Deutsche Bank. In cases where at least one Brazil based analyst (identified by a phone number starting with +55 country code) has taken part in the preparation of this research report, the Brazil based analyst whose name appears first assumes primary responsibility for its content from a Brazilian regulatory perspective and for its compliance with CVM Instruction # 483.
EU countries: Disclosures relating to our obligations under MiFiD can be found at http://www.globalmarkets.db.com/riskdisclosures.
Japan: Disclosures under the Financial Instruments and Exchange Law: Company name - Deutsche Securities Inc. Registration number - Registered as a financial instruments dealer by the Head of the Kanto Local Finance Bureau (Kinsho) No. 117. Member of associations: JSDA, Type II Financial Instruments Firms Association, The Financial Futures Association of Japan, Japan Investment Advisers Association. Commissions and risks involved in stock transactions - for stock transactions, we charge stock commissions and consumption tax by multiplying the transaction amount by the commission rate agreed with each customer. Stock transactions can lead to losses as a result of share price fluctuations and other factors. Transactions in foreign stocks can lead to additional losses stemming from foreign exchange fluctuations. "Moody's", "Standard & Poor's", and "Fitch" mentioned in this report are not registered credit rating agencies in Japan unless “Japan” or "Nippon" is specifically designated in the name of the entity.
Russia: This information, interpretation and opinions submitted herein are not in the context of, and do not constitute, any appraisal or evaluation activity requiring a license in the Russian Federation.

Deutsche Bank AG/London

European locations

Deutsche Bank AG London
1 Great Winchester Street
London EC2N 2EQ

Tel: (44) 20 7545 8000

Deutsche-Bank AG,
3, Avenue de Friedland
75008 Paris Cedex 8
France
Tel: (33) 1 44 95 64 00

Deutsche Bank AG
Equity Research
Große Gallusstraße 10-14
60272 Frankfurt am Main
Germany
Tel: (49) 69 910 00

Deutsche Bank Sim S.p.a
Via Santa Margherita 4
20123 Milan
Italy

Tel: (39) 0 24 024 1

Deutsche Bank AG
Herengracht 450
1017 CA Amsterdam
Netherlands

Tel: (31) 20 555 4911

Deutsche Securities
S.V.B, S.A.
Paseo de la Castellana,
18 Entreplanta
28046 Madrid, Spain
Tel: (34) 91 335 5900

Deutsche Bank AG
Stureplan 4 A, Box 5781
S-114 87 Stockholm
Sweden

Tel: (46) 8 463 5500

Deutsche Bank AG
Uraniastrasse 9
PO Box 7370
8023 Zürich
Switzerland
Tel: (41) 1 224 5000

Deutsche Bank AG, Helsinki
Kaivokatu 10 A, P.O.Box 650
FI-00101 Helsinki
Finland

Tel: (358) 9 25 25 25 0

Deutsche Bank AG
Hohenstaufengasse 4
1010 Vienna
Austria

Tel: (43) 1 5318 10

Deutsche Bank Ltd
Aurora business park
82 bld.2 Sadovnicheskaya street
Moscow, 115035
Russia
Tel: (7) 495 797-5000

Deutsche Bank AG, Warsaw
al.Armii Ludowej 26
Budynek FOCUS
00-609 Warsaw
Poland
Tel: (48) 22 579 87 00

Deutsche Bank AG, Turkey
Eski Buyukdere Cad. Tekfen Tower
No:209 Kat:17-18
TR-34394 Istanbul
Tel: (90) 212 317 01 00

Deutsche Bank AG, Greece
23A Vassilissis Sofias Avenue
6th Floor
10674 Athens, Greece
Tel: (30) 210 72 56 150

International locations

Deutsche Bank Securities Inc.
60 Wall Street
New York, NY 10005
United States of America
Tel: (1) 212 250 2500

Deutsche Bank AG London
1 Great Winchester Street
London EC2N 2EQ
United Kingdom
Tel: (44) 20 7545 8000

Deutsche Bank AG
Große Gallusstraße 10-14
60272 Frankfurt am Main
Germany
Tel: (49) 69 910 00

Deutsche Bank AG
Deutsche Bank Place
Level 16
Corner of Hunter & Phillip Streets
Sydney, NSW 2000
Australia
Tel: (61) 2 8258 1234

Deutsche Bank AG
Filiale Hongkong
International Commerce Centre,
1 Austin Road West,Kowloon,
Hong Kong
Tel: (852) 2203 8888

Deutsche Securities Inc.
2-11-1 Nagatacho
Sanno Park Tower
Chiyoda-ku, Tokyo 100-6171
Japan
Tel: (81) 3 5156 6770

Global Disclaimer

The information and opinions in this report were prepared by Deutsche Bank AG or one of its affiliates (collectively "Deutsche Bank"). The information herein is believed to be reliable and has been obtained from public sources believed to be reliable. Deutsche Bank makes no representation as to the accuracy or completeness of such information.

Deutsche Bank may engage in securities transactions, on a proprietary basis or otherwise, in a manner inconsistent with the view taken in this research report. In addition, others within Deutsche Bank, including strategists and sales staff, may take a view that is inconsistent with that taken in this research report.

Opinions, estimates and projections in this report constitute the current judgement of the author as of the date of this report. They do not necessarily reflect the opinions of Deutsche Bank and are subject to change without notice. Deutsche Bank has no obligation to update, modify or amend this report or to otherwise notify a recipient thereof in the event that any opinion, forecast or estimate set forth herein, changes or subsequently becomes inaccurate. Prices and availability of financial instruments are subject to change without notice. This report is provided for informational purposes only. It is not an offer or a solicitation of an offer to buy or sell any financial instruments or to participate in any particular trading strategy. Target prices are inherently imprecise and a product of the analyst judgement.

As a result of Deutsche Bank's March 2010 acquisition of BHF-Bank AG, a security may be covered by more than one analyst within the Deutsche Bank group. Each of these analysts may use differing methodologies to value the security; as a result, the recommendations may differ and the price targets and estimates of each may vary widely.

In August 2009, Deutsche Bank instituted a new policy whereby analysts may choose not to set or maintain a target price of certain issuers under coverage with a Hold rating. In particular, this will typically occur for "Hold" rated stocks having a market cap smaller than most other companies in its sector or region. We believe that such policy will allow us to make best use of our resources. Please visit our website at http://gm.db.com to determine the target price of any stock.

The financial instruments discussed in this report may not be suitable for all investors and investors must make their own informed investment decisions. Stock transactions can lead to losses as a result of price fluctuations and other factors. If a financial instrument is denominated in a currency other than an investor's currency, a change in exchange rates may adversely affect the investment. Past performance is not necessarily indicative of future results. Deutsche Bank may with respect to securities covered by this report, sell to or buy from customers on a principal basis, and consider this report in deciding to trade on a proprietary basis.

Unless governing law provides otherwise, all transactions should be executed through the Deutsche Bank entity in the investor's home jurisdiction. In the U.S. this report is approved and/or distributed by Deutsche Bank Securities Inc., a member of the NYSE, the NASD, NFA and SIPC. In Germany this report is approved and/or communicated by Deutsche Bank AG Frankfurt authorized by the BaFin. In the United Kingdom this report is approved and/or communicated by Deutsche Bank AG London, a member of the London Stock Exchange and regulated by the Financial Services Authority for the conduct of investment business in the UK and authorized by the BaFin. This report is distributed in Hong Kong by Deutsche Bank AG, Hong Kong Branch, in Korea by Deutsche Securities Korea Co. This report is distributed in Singapore by Deutsche Bank AG, Singapore Branch, and recipients in Singapore of this report are to contact Deutsche Bank AG, Singapore Branch in respect of any matters arising from, or in connection with, this report. Where this report is issued or promulgated in Singapore to a person who is not an accredited investor, expert investor or institutional investor (as defined in the applicable Singapore laws and regulations), Deutsche Bank AG, Singapore Branch accepts legal responsibility to such person for the contents of this report. In Japan this report is approved and/or distributed by Deutsche Securities Inc. The information contained in this report does not constitute the provision of investment advice. In Australia, retail clients should obtain a copy of a Product Disclosure Statement (PDS) relating to any financial product referred to in this report and consider the PDS before making any decision about whether to acquire the product. Deutsche Bank AG Johannesburg is incorporated in the Federal Republic of Germany (Branch Register Number in South Africa: 1998/003298/10). Additional information relative to securities, other financial products or issuers discussed in this report is available upon request. This report may not be reproduced, distributed or published by any person for any purpose without Deutsche Bank's prior written consent. Please cite source when quoting.