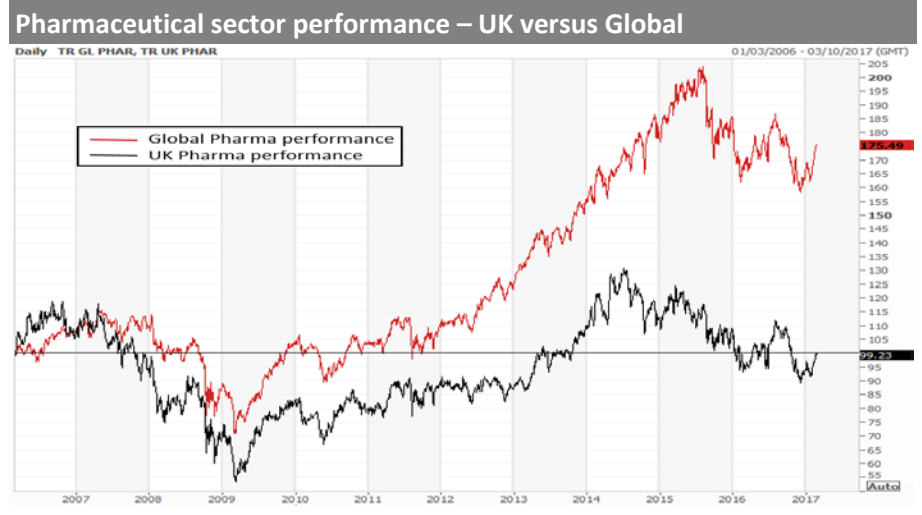


Global Pharmaceuticals

2016 industry statistics

The annual company reporting season is always an exciting period and, during the past few weeks, most of the major pharmaceutical companies have reported results for 2016. This has provided us with the opportunity to update our industry statistics and drug database which always generates some interesting observations. For an industry that requires a long investment cycle, decisions made many years' ago have consequences on current financial performance. Being able to look at performance over 20 years highlights how strategic decisions have panned out.

- ▶ **Global market:** The value of the global prescription drug market was estimated to be \$816bn in 2016, representing underlying growth of 4.9%. Strength of the USD, particularly against the JPY, dented the reported figure by about \$12bn.
- ▶ **US market:** The US market was a key driver of growth, rising 5.6% to \$320bn in 2016, from \$303bn in 2015. This was due, in part, to the positive trend in NME approvals by the FDA over the last three years, although this was halted in 2016.
- ▶ **Company ranking:** Pfizer has returned to the #1 ranked company both globally and in the US with a market share of 5.6% and 6.8%, respectively, having adopted the strategy of being the leading industry consolidator over 20 years.
- ▶ **Biopharmaceuticals:** Drugs classified as biopharmaceuticals (ca.130 + vaccines) had reported sales of \$197bn in 2016, with above average growth of +7.6%. These drugs now represent 24% of the global drug market. Within this segment, the 61 approved drugs derived from antibodies had sales of \$82bn (+15.4%).
- ▶ **Top drugs:** The biggest drug in 2016 was Humira (AbbVie) with ex-factory sales of \$16.1bn (+14%). The top 10 drugs in the world represented 25% of the entire market. On a cumulative basis, the best-selling drug ever remains Lipitor (\$152bn).
- ▶ **R&D investment:** Investment in R&D is key to future success. The top 15 companies invested \$86.0bn in pharma R&D in 2016, representing 20.5% of Rx drug sales. The highest spender was Roche at \$10.3bn (22.6% of Rx sales).



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Table of contents

2016 Industry statistics	3
2016 Global pharmaceutical market	3
2016 Company highlights	5
Strategy has been key	6
All change for UK companies.....	7
Focus on the US market	9
FDA approvals in 2016.....	10
Top selling drugs	11
Top 10 drugs in 2016.....	11
Biopharmaceuticals	12
Cumulative sales – an alternative analysis	13
About the authors	14
Disclaimer	15
Hardman Team	16

2016 Industry statistics

Annual company reporting period is always an exciting time...

...and always throws up some interesting statistics

Data compiled from 40 companies representing ca.75% of the global market...

...and over 90% of the US market

2016 Global market estimated at US\$816bn...

...with underlying growth of +4.9%...

...largely driven by US market growth of +5.6% to USD320bn

It is important to understand the industry in which our contracted companies, generally of small- to mid- sized market capitalisation, operate. Given that most of the major pharmaceutical companies have reported full-year results for 2016 over the last few weeks, we have taken the opportunity to update our industry statistics and make the first cut of global rankings. For an industry that requires a long investment cycle – it still takes on average 10 years from discovery to launch of a new drug – decisions made many years ago have important consequences on current financial results. Therefore, looking back at operational performance over 20 years reveals how different company strategies have panned out.

When we write a research report, it is imperative that we outline the commercial market opportunity that the company's (often disruptive) technology is targeting. While such work requires significant research, it often constitutes only a very small part of the overall report. It has the advantage, however, of providing us with a global dataset that is reliable and independent of third party input.

Pharmaceutical sales are defined as anything that requires a prescription (Rx) and specifically excludes Over-The-Counter (OTC) and consumer products. It does include generic drugs and biosimilars.

All the data, going back as far as 1988, are based on ex-factory sales reported by companies and excludes all discounts and government rebates, such as Medicaid and Medicare. All reported numbers are converted into USD at daily average exchange rates – available from the Bank of England website. These data have, therefore, been compiled consistently and with great care so that direct comparisons among companies can be made.

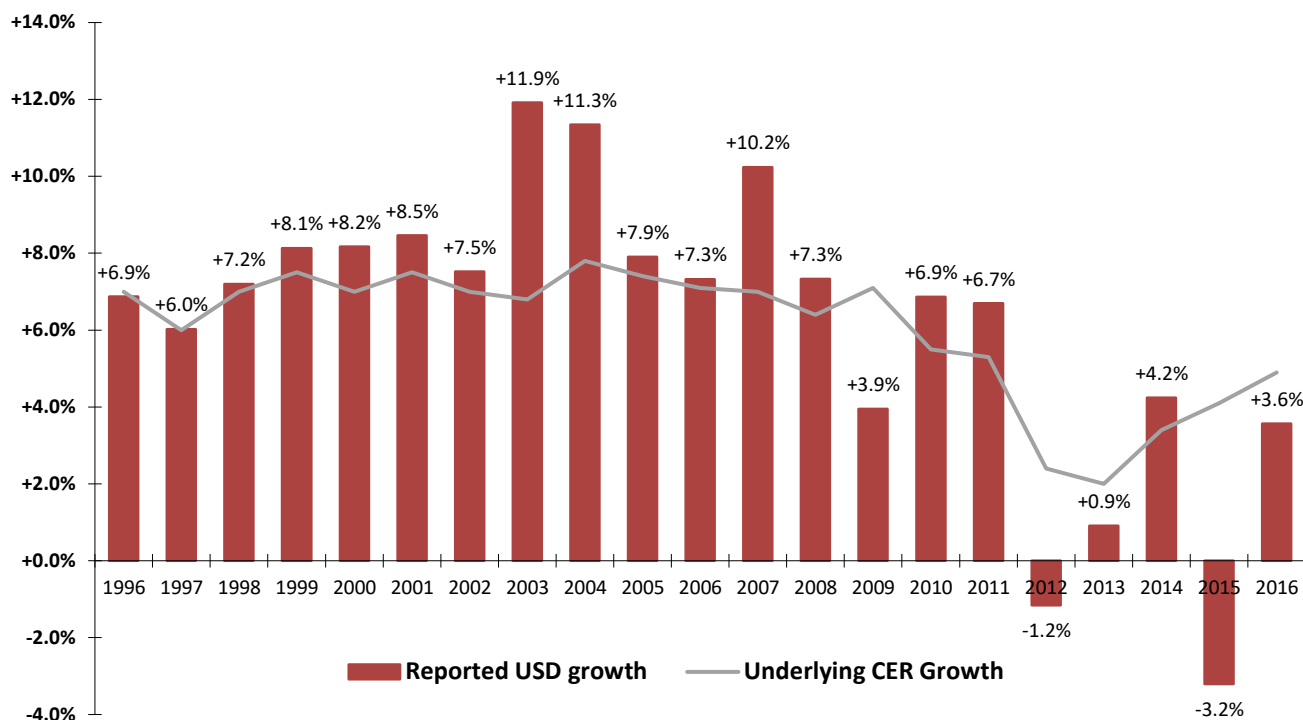
We have based our analysis on the accounts of around 40 multinational companies, which cover ca.75% of the global pharmaceutical market and 90% of the US drug market. Market share statistics have been calculated from our provisional estimate for the global prescription drug market, which cannot be finalised until after the Japanese drug companies and Boehringer Ingelheim report in May.

2016 Global pharmaceutical market

Hardman & Co estimates that the worldwide prescription drug market had underlying growth of +4.9% from \$786bn 2015 to a reported level of US\$816bn in 2016. The last few years have seen a positive trend in the underlying rate of growth for the industry. Despite a perception that the USD was very strong last year, in reality it has been stable against many currencies, including the EUR, Swiss Franc (CHF) and Danish Krone (DKK). In contrast, it has been strong against the GBP and JPY, which have both declined by >10%. On a constant currency basis, we estimate that the global market would have been US\$828bn.

The US market was itself a key driver of growth. Based on companies that have reported to date, Hardman & Co estimates that the US prescription drug market had growth of +5.6% to \$320bn, up from \$303bn in 2015, and currently represents 39% of the global market. This may well have been influenced by positive trends in FDA approvals in the last three years, which halted abruptly in 2016 with only 22 New Molecular Entity (NME) approvals by the FDA.

Global prescription drug market growth – 1996-2016



Source: Hardman & Co Life Sciences Research

*Despite some pressures...**...2016 was a very satisfactory year for the industry*

In general, 2016 was a very satisfactory year for the worldwide pharmaceutical industry, with underlying growth running close to +5% despite some natural pressures. This growth rate was achieved despite a background of considerable political uncertainty, government and media attention on drug pricing – particularly in relation to older drugs – plus an increasing number of biosimilar approvals. However, we firmly believe that innovation will still win out in the long-term, as evidenced by strong sales growth in biopharmaceuticals (+8%), which was led by antibody-derived drugs (+15%), and explains the continued heavy investment in R&D. Hardman & Co estimates that the top 15 companies had ca.53% of the world market in 2016.

Investment in R&D remains strong

- ▶ Top 15 companies invested 20.5% of pharmaceutical sales back into new drug development
- ▶ Average spend of the top 15 companies was \$5.7bn – range \$10.3bn (Roche) to \$3.6bn (Takeda)
- ▶ Total R&D spend of the top 15 companies was \$86.0bn out of a total estimated spend of \$120bn by 37 companies

*Investment in R&D remains very strong...**...with companies investing 20.5% of pharma sales back into pharma R&D*

Companies are continuing to invest heavily in their futures, as all managements can see that successful innovation pays off (see pages 11-13). In 2016, the top 15 R&D spenders increased investment by +5.8% to \$86.0bn (\$81.3bn in 2015). Over the last 10 years, the top 15 R&D investors have increased spend at +3.4% CAGR from \$61.6bn (18.7% of pharma sales) to \$86.0bn (20.5%) in 2016. The highest spenders were Celgene (40.0% of sales), Bristol-Myers Squibb (27.9%), and AstraZeneca (27.6%), with Gilead (12.5%) and Pfizer (16.0%) the lowest. It should be noted that the 15 constituent companies that comprise the top 15 is different each year.

2016 Company highlights

Pfizer ranked #1 in world and the US

- ▶ **Pfizer** has returned to the #1 position, both globally and in the US, with market shares of 5.56% and 6.79%, respectively. Given its leading role in industry consolidation over the last 20 years, it has products in most drug categories. However, the vast majority of its sales growth was derived from three recently launched kinase inhibitors. It will be interesting to see whether Pfizer can maintain its position in the absence of any approved antibody-derived drugs.

Gilead slipped back due to competition

- ▶ **Gilead Sciences** slipped to #7 in 2016 (from #6 in 2015) globally and to #3 (from #1) in the US following the launch of new hepatitis drugs by major competitors. Whilst many of these new drugs still need to be used in combination with Gilead's products, this slippage looks set to continue in 2017, with management guidance for sales to fall a further 22-24%.

Shire up to world #14 on a pro-forma basis

- ▶ **Shire Pharma** is a new entrant to the top 20 following completion of its acquisition of Baxalta in June 2016. On a *pro forma* basis, Shire was ranked #17 in 2016 with 1.65% market share. In the US, it is now ranked 14th with 2.77% market share. Moreover, performance is not just acquisition related, with strong organic growth within its existing drug portfolio.

Novo has benefited from the rising incidence of diabetes

- ▶ **Novo-Nordisk** managed to stay in the top 15 in the US and globally despite encountering a difficult year. Although there is increased recognition that obesity is a global epidemic and a cause of increasing incidence of diabetes, there is also greater awareness that insulin analogues that offer marginal benefits do not deserve the price premiums being sought. Particularly, questions are being asked as to why prices of Novo's insulin analogues in the US are multiple times those of the same drug in Europe.

AstraZeneca no longer in the top 15 in the US

- ▶ **AstraZeneca** has been another significant mover – albeit in a downward direction. Ten years ago, AZN was ranked #6 both worldwide and in the US with ca.5% market share. By 2015, it had slipped back to 9th and 12th respectively. Further sales erosion in 2016 has seen AZN fall to #11 globally, and more importantly, down to #16 in the US, where its market share (2.3%) is now lower than its global market share (2.6%).

Pharmaceutical industry – Global ranking 2001-2016

#	2001	Share	2006	Share	2011	Share	2016	Share
1.	GlaxoSmithKline	6.90%	Pfizer	7.55%	Pfizer	6.93%	Pfizer	5.56%
2.	Pfizer	6.72%	GlaxoSmithKline	6.30%	Novartis	6.05%	Novartis	5.25%
3.	Merck & Co	5.91%	Sanofi-Aventis	6.15%	Merck & Co	5.29%	Roche	4.88%
4.	AstraZeneca	4.47%	Novartis	4.93%	Sanofi-Aventis	5.11%	Merck & Co	4.32%
5.	Aventis	4.40%	Roche	4.59%	Roche	4.73%	Sanofi	4.14%
6.	Johnson & Johnson	4.14%	AstraZeneca	4.45%	GlaxoSmithKline	4.56%	Johnson & Johnson	4.11%
7.	Novartis	3.73%	Merck & Co	4.24%	AstraZeneca	4.22%	Gilead Sciences	3.68%
8.	Bristol-Myers Squibb	3.67%	Johnson & Johnson	4.02%	Johnson & Johnson	3.12%	GlaxoSmithKline	3.42%
9.	Pharmacia	3.33%	Lilly	2.56%	Abbott Labs	2.87%	AbbVie	3.15%
10	Lilly	3.02%	Wyeth	2.48%	Lilly	2.81%	Amgen	2.69%
11.	Roche	2.81%	Abbott Labs	2.43%	Bristol-Myers Squibb	2.72%	AstraZeneca	2.62%
12.	American Home Prods.	2.74%	Bristol-Myers Squibb	2.39%	Takeda	2.18%	Teva	2.37%
13.	Schering-Plough	2.33%	Amgen	2.39%	Teva	2.04%	Lilly	2.22%
14.	Takeda	2.29%	Bayer	2.21%	Amgen	1.96%	Bristol-Myers Squibb	2.17%
15.	Abbott Labs	2.28%	Takeda	1.99%	Boeh. Ingelheim	1.80%	Novo Nordisk	2.04%
		58.7%		58.7%		56.4%		52.6%

Source: Hardman & Co Life Sciences Research

Strategy has been key

History suggests that management should make more external investments in new technologies

Strategy has been all important. Management of the major players 10-15 years ago often took the easy option of acquiring companies with established products, with the sole intention of creating 'fat' and then reducing excess costs. Instead, they perhaps should have taken the riskier option of acquiring new technologies with the aim of improving the product pipeline. Ironically, they probably thought that the riskier strategy put their jobs at risk, which many ended up losing anyway!

Innovation is key to long-term success

The table above highlights the changes in the top 15 ranked drug companies every five years over a 15-year period. Movement in a positive direction has generally been the direct result of successful new drug introductions – for example Abbott Labs /AbbVie (Humira) and Gilead Sciences (Harvoni and Sovaldi) – or from steady growth in prevalence of certain medical conditions – e.g. Novo Nordisk due to obesity/diabetes.

Patent expiry has a profound impact

In the opposite direction, losses of significant market share and position in the ranking have been the consequence of patent expiry on significant drugs that could not be compensated by new drug launches emanating from the R&D pipeline – e.g. GlaxoSmithKline, AstraZeneca and Bristol-Myers Squibb.

Some in the latter category have chosen a defensive consolidation strategy to remove costs in an attempt to protect operating margins, with variable degrees of success – e.g. Pfizer and Merck & Co.

Pfizer

PFE has returned to #1...

Pfizer is an interesting case study. The company has consistently been an industry consolidator, usually from a defensive position, and has risen from #22 back in 1996 to #1 again in 2016. Its history is shown in the following table. The market share of the combined entity equates to around 12%, but today it has just 5.6% of the world market.

...but has lost a lot of market share...

The building of Pfizer		
Date	Event	Market share
1994	Pfizer (ranked #22)	2.7%
1995	Acquisition of American Cyanamid	1.3%
1995	Upjohn merged with Pharmacia	
2000	Pharmacia acquires Searle (Monsanto)	
2000	Acquisition of Warner-Lambert	2.6%
2002	Acquisition of Pharmacia	3.3%
2010	Acquisition of Wyeth/American Home Products	2.0%
	Pfizer accumulated market share	11.9%
2016	Pfizer today ranked #1	5.6%
		-6.3%

Source: Hardman & Co Life Sciences Research

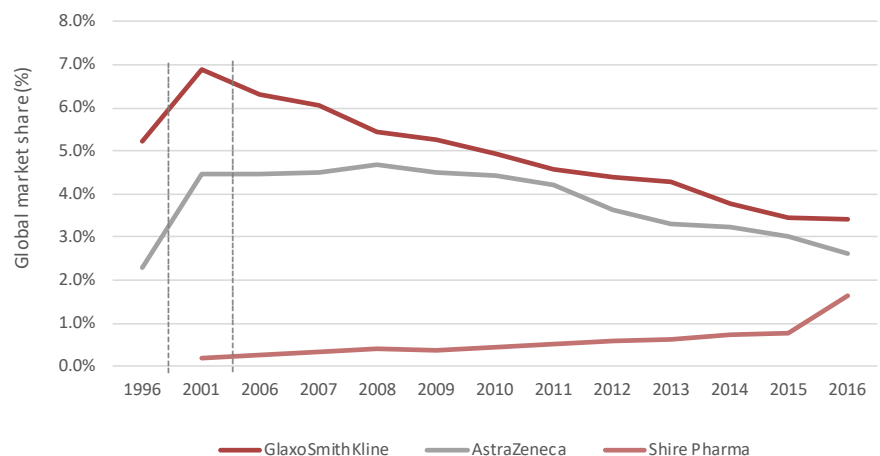
...due, in part, to limited exposure to biopharmaceuticals

Pfizer has a vast portfolio of drugs covering many medical conditions and disease states. As highlighted earlier, in 2016 the vast majority of its sales growth was derived from three recently launched kinase inhibitors – Ibrance (metastatic breast cancer), Xeljanz (rheumatoid arthritis) and Xalkori (NSCLC). These drugs are Pfizer's participation in the fast growing biopharmaceuticals segment of the market (see page 12). However, despite its global and US leading position, Pfizer does not have any representation in the antibody segment of the market.

All change for UK companies

The position in the world ranking for the UK companies could not be more different, with GlaxoSmithKline and AstraZeneca moving in one direction and Shire Pharma becoming an increasing important player. This is highlighted in the market share trend demonstrated in the following graphic.

Global market share – UK companies in world top 15



Source: FDA; Washington Analysis Group; Hardman & Co Life Sciences Research

GlaxoSmithKline

GSK has fallen from #1 to #8 over 15 years...

...despite investing ca.\$60bn in R&D

How the mighty have fallen! It seems incredible that GlaxoSmithKline was the #1 ranked drug company in the world in 2001 – sales of US\$24bn gave it 6.9% market share. Since then, its position has steadily eroded, and, whilst sales have risen to USD27.8bn (CAGR +0.8%), this is well below the global industry's +5.6% compound growth rate. In 2016, GSK remained steady at #8 in the world, although Advair generic competition seems set to impact in 2017. Like Pfizer, it has limited exposure, except for vaccines, to the biopharmaceuticals segment, although it is hoped that recent approvals (Nucala, Mekinist, Entyvio) might start to change that.

AstraZeneca

AZN is no longer in the top 15 in the US market

On the one hand AstraZeneca is similar to GSK, in that the merger of Astra with Zeneca was partly defensive, increasing market share and allowing the removal of costs; on the other hand, unlike GSK, AstraZeneca has actively sought new technologies that it did not have in-house that were likely to change the future landscape for drugs. In May 2006, it bought Cambridge Antibody Technologies to provide a position in the emerging field of therapeutic antibodies and followed this in June 2007 with the acquisition of MedImmune, which took the company into biologics and vaccines. It has supplemented these bigger deals with some in-licensing of products. Despite this, it has struggled overcome lost sales through patent expiry and has slipped down both global and, more importantly, US rankings.

On the other hand, Shire's buy-and-build approach has been very rewarding

Shire Pharmaceuticals

In contrast, over the same period of time, Shire has continued its strategy of buy-and-build, adding specialist therapeutic areas and technologies through licensing deals and acquisitions that complemented and added to those that it already possessed. In 2006, Shire was ranked a lowly #37. Its acquisition of Baxalta coupled with organic growth has propelled the company in 2016 to #17 on a worldwide *pro forma* basis and #14 in the US.

Pharmaceutical industry – 2016 global ranking

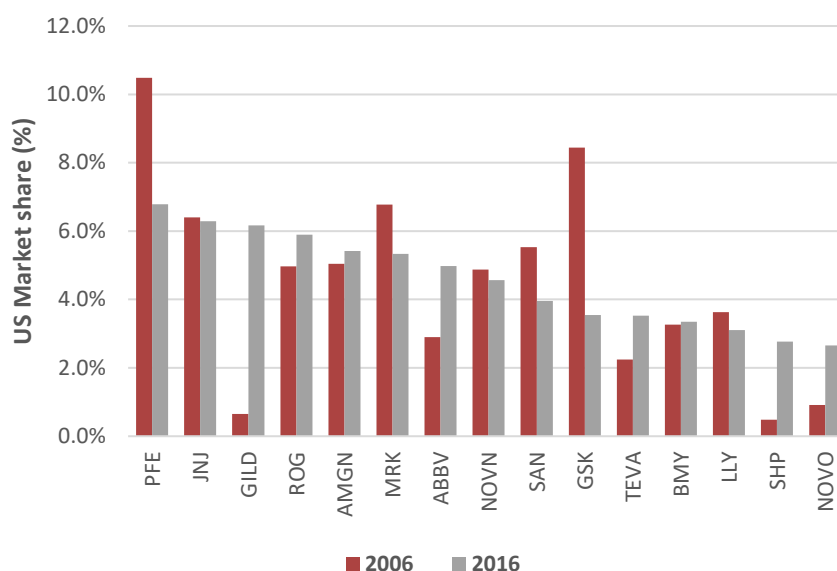
--Global Rank --		Company	Sales	----- Market share -----		
2006	2016		CAGR	2006	2016	Δ
1	1	Pfizer	+0.3%	7.85%	5.56%	-2.29%
4	2	Novartis	+4.1%	5.12%	5.25%	+0.12%
5	3	Roche	+4.1%	4.77%	4.88%	+0.11%
7	4	Merck & Co	+3.6%	4.41%	4.32%	-0.09%
3	5	Sanofi	-0.5%	6.39%	4.14%	-2.25%
8	6	Johnson & Johnson	+3.7%	4.18%	4.11%	-0.07%
31	7	Gilead Sciences	+27.7%	0.46%	3.68%	+3.22%
2	8	GlaxoSmithKline	-2.8%	6.64%	3.42%	-3.22%
11	9	AbbVie	+6.2%	2.53%	3.15%	+0.62%
13	10	Amgen	+4.7%	2.49%	2.69%	+0.20%
6	11	AstraZeneca	-1.9%	4.62%	2.62%	-2.00%
18	12	Teva	+9.5%	1.40%	2.37%	+0.97%
9	13	Lilly	+2.0%	2.66%	2.22%	-0.44%
12	14	Bristol-Myers Squibb	+2.5%	2.49%	2.17%	-0.31%
22	15	Novo Nordisk	+9.8%	1.17%	2.04%	+0.87%
Global Rx market			+3.9%	57.2%	52.6%	-4.6%

Source: Company reports; Hardman & Co Life Sciences Research

Focus on the US market

- ▶ **Pfizer** has returned to the #1 position in 2016 with 6.79% market share
- ▶ **Gilead Sciences** slips to #3 as competition arrived in the hepatitis C market
- ▶ **Shire Pharma** has entered the top 15 on a *pro forma* basis on the back of organic growth coupled with the acquisition of Baxalta
- ▶ **AstraZeneca** is no longer among the top 15 drug companies in the US – now ranked #16
- ▶ The US market is provisionally estimated at \$320bn and our data analysis covers 90% of this market

US ranking 2006-2016 – Winners & losers



Source: Hardman & Co Life Sciences Research

US pharmaceutical industry – 2016 ranking

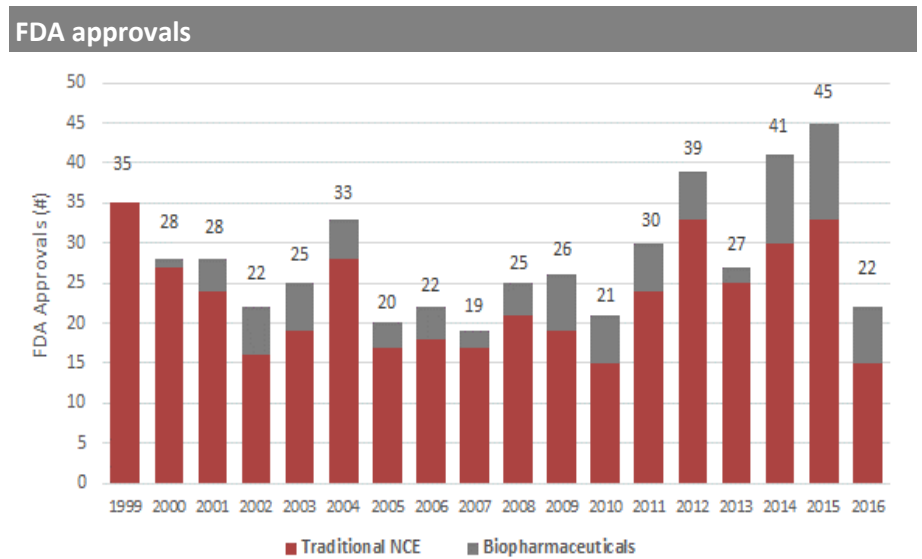
----US Rank ----		Company	Sales CAGR	----- Market share -----		
2006	2016			2006	2016	Δ
1	1	Pfizer	-0.9%	10.48%	6.79%	-3.69%
4	2	Johnson & Johnson	+3.3%	6.41%	6.29%	-0.12%
27	3	Gilead Sciences	+29.7%	0.65%	6.17%	+5.52%
8	4	Roche	+5.3%	4.97%	5.90%	+0.93%
7	5	Amgen	+4.3%	5.04%	5.41%	+0.37%
3	6	Merck & Co	+1.1%	6.78%	5.34%	-1.44%
13	7	AbbVie	+9.3%	2.90%	4.98%	+2.08%
9	8	Novartis	+2.9%	4.88%	4.56%	-0.31%
5	9	Sanofi	+0.1%	5.53%	3.96%	-1.57%
2	10	GlaxoSmithKline	-5.1%	8.44%	3.55%	-4.90%
14	11	Teva	+8.3%	2.24%	3.53%	+1.28%
12	12	Bristol-Myers Squibb	+3.8%	3.26%	3.35%	+0.09%
10	13	Lilly	+2.0%	3.63%	3.11%	-0.52%
31	14	Shire Pharma	+23.2%	0.49%	2.77%	+2.28%
23	15	Novo Nordisk	+15.2%	0.91%	2.66%	+1.74%
US Rx market			+3.5%	66.6%	68.3%	+1.7%

Source: Company reports; Hardman & Co Life Sciences Research

The last decade is ideal for highlighting the different strategies employed by company management teams. The chart above and following table show the ranking of the top 15 companies by US Rx drug sales in 2016 compared to 2015, emphasising the change in market share over this period of time.

FDA approvals in 2016

- ▶ Only 22 New Molecular Entities (NME) approved by FDA in 2016, down 51%
- ▶ 15 (68%) were small molecules and seven (32%) were biopharmaceuticals, this compares with 33 and 12 respectively in 2015
- ▶ In addition, there were 633 generics approved in 2016, the highest ever total
- ▶ At the end of 2016, there were 29 NME filed, pending FDA review, compared with 20 at the beginning of 2016



Source: FDA; Washington Analysis Group; Hardman & Co Life Sciences Research

While this report is not about forecasts, we are conscious of a number of positive trends and negative pressures on the industry.

Top selling drugs

- ▶ The biggest drug in 2016 was **Humira** (AbbVie), with sales of \$16.1bn (+14%)
- ▶ The top 10 drugs in 2016 accounted for 25% of the world market
- ▶ **Biopharmaceuticals** represented 24% of the world market in 2016 with sales of \$197bn, with growth of +8%
- ▶ Within biopharmaceuticals, drugs derived from **antibodies** were the growth drivers, with 2016 sales of \$82bn, +15%
- ▶ The biggest ever drug in history is **Lipitor**, with cumulative ex-factory sales since launch of \$152bn

Top 10 drugs in 2016

Top 10 drugs in world account for 25% of the market...

...with Humira alone representing 2%

In 2016, the top 10 best-selling drugs recorded ex-factory sales of \$78.3bn and represented 25% of the global pharmaceutical market. Way out in front is Humira (adalimumab; AbbVie), with reported sales of \$16.1bn and growth of +14.7%. Since it was launched 14 years ago, this drug has generated cumulative sales of \$94.7bn. Humira was the first 'humanised' monoclonal antibody (Mab) to be approved by the FDA, and is indicated for the treatment of autoimmune diseases such as rheumatoid arthritis, Crohn's disease and psoriasis. However, its patent expired in the US back in December 2016, and will expire in April 2018 in EU countries. Although the FDA has approved a biosimilar (Amjevita) from Amgen, it is the subject of patent litigation and the earliest that it can be launch is March 2017.

Global top 10 selling drugs in 2016

Drug	Primary indication	Marketer	Sales (\$m)	Growth (%)
Humira	Arthritis	AbbVie	16,078	+14.7%
Harvoni	Hepatitis C	Gilead Sciences	9,081	-34.5%
Rituxan/MabThera	Non-Hodgkins lymphoma	Roche	7,411	+1.1%
Revlimid	Multiple myeloma	Celgene	6,974	+20.2%
Remicade	Arthritis	Johnson & Johnson	6,966	+6.2%
Avastin	Cancer	Roche	6,886	-0.9%
Herceptin	Cancer	Roche	6,885	+1.3%
Lantus	Diabetes I	Sanofi	6,321	-10.9%
Enbrel	Arthritis	Amgen	5,965	+11.2%
Prevnar	Pneumococcal vaccine	Pfizer	5,718	-8.4%

Source: Hardman & Co Life Sciences Research

Biosimilars are on the way

In third place is Rituxan/MabThera (rituximab), Roche's leading drug for cancer, with sales of \$7.4bn in 2016. This was one of the first Mabs to be approved and launched (1997). However, growth is slowing and the EU has recently (February 2017) approved a biosimilar version (Truxima) from South Korean company, Celltrion.

Successful innovation can transform financial performance

We would also highlight Revlimid (lenalidomide) for multiple myeloma for its exceptional growth rate of +20.2% to \$7.0bn and Harvoni (ledipasvir + sofosbuvir), for treatment of hepatitis C with sales of \$9.1bn (-34.5%), both of which have been transformational for their respective developers, Celgene and Gilead Sciences. These two drugs highlight how successful R&D can change a company's fortunes and, if possible, how important it is to retain the commercial rights for shareholders.

For so long, vaccines were considered to be an uninteresting area for the drug majors. American Home products, now part of Pfizer, persevered and developed Prevnar, the pneumococcal vaccine, which was ranked an impressive #10 last year.

Biopharmaceuticals

Biopharmaceutical market was \$197bn in 2016...

with growth of 7.6%

Within the overall global prescription market, drugs classified as biopharmaceuticals (ca.130 + vaccines) had reported sales of \$197bn in 2016, and now represent 24% of the entire market. The growth rate was above average at +7.6%. It should be pointed out that these are provisional numbers, given the later reporting of results by some companies, but we are only awaiting sales confirmation from 11% of drugs in this segment. Every year since 2000, biopharmaceuticals have represented a greater proportion of the global pharmaceutical market. Over the last 10 years, the biopharmaceutical market has grown at a compound rate of +10.8%, compared to +2.0% for all other drugs.

For clarification, we classify a biopharmaceutical as a drug derived from biological sources, which may be through extraction or semi-synthesized and would include the likes of monoclonal antibodies, vaccines and blood products.

Evolution of global biopharmaceuticals market – 2001 to 2016						
2016 Rank	Drug	2001	2006	2011	2016	CAGR 2006-2016
1	Insulin/analogues	3,518	9,721	19,830	25,597	+10%
2	Humira	0	2,045	7,932	16,078	+23%
3	Enbrel	808	4,477	7,886	9,211	+7%
4	Rituxan/MabThera	1,005	3,862	6,772	7,411	+7%
5	Remicade	887	3,013	5,492	6,966	+9%
6	Avastin	0	2,364	5,968	6,886	+11%
7	Herceptin	478	3,134	5,922	6,885	+8%
8	Human Growth Hormone	1,825	3,880	5,332	5,904	+4%
9	Interferons (α & β)	3,411	6,647	9,161	5,634	-2%
10	Erythropoietin	6,698	9,812	6,366	5,530	-6%
Total biopharmaceuticals		28,642	70,536	138,147	196,500	+12%
% Global market		8.1%	12.2%	17.7%	24.1%	

Source: Hardman & Co Life Sciences Research

There are 61 approved drugs derived from antibodies...

...that had sales of \$82bn in 2016...

...after growth of 15.4%

Second generation mAb products and derivatives are now needed

Continuing rise of antibody-derived therapeutics

In 2016, drugs derived from monoclonal antibodies were the fastest growing sub-segment of the market with growth of +15.4% to \$81.9bn and have grown to represent 42% of biopharmaceutical sales and 10.0% of the entire global market for prescription drugs. The first, ReoPro (abciximab), was launched in 1995 and there are now 61 regulatory-approved mAb drugs on the market. The following table shows the ranking of the top 10 drugs by ex-factory sales. The table also shows that drugs derived from antibodies have generated cumulative sales approaching a staggering \$564bn! These figures are expected to rise further in coming years given the large numbers currently in clinical trials.

Drugs based on monoclonal antibodies cover a big spread of diseases and have revolutionised the treatment of autoimmune disease such as arthritis (rheumatoid and psoriatic) and cancer. While arthritis drugs are the biggest sellers, 35 (58%) of the 61 approved drugs are for treatment of different cancers. However, it is thought that the currently approved, and waiting for approval, drugs represent the success of the first generation of antibody-based products, and that a new generation of engineered antibodies based on a variety of biotech platforms is required to produce new therapeutics with enhanced mechanisms of action and/or improved pharmacokinetics and safety profiles, including:

- ▶ Bi-specific and Tri-specific antibodies
- ▶ Antibody-drug conjugates

Top 10 antibody drugs – 2016

2016 Rank	Drug	Generic name	Company	2015 (\$m)	2016 (\$m)	Growth (%)	Cumulative (\$m)
1	Humira	adalimumab	AbbVie	14,012	16,078	+15%	94,687
2	Rituxan/MabThera	rituximab	Roche	7,333	7,411	+1%	80,950
3	Remicade	infliximab	Johnson & Johnson	6,561	6,966	+6%	66,498
4	Avastin	bevacizumab	Roche	6,948	6,886	-1%	64,091
5	Herceptin	trastizumab	Roche	6,796	6,885	+1%	66,641
6	Opdivo	nivolumab	Bristol-Myers Squibb	475	3,774	+695%	4,255
7	Stelara	ustekinumab	Johnson & Johnson	2,474	3,232	+31%	11,438
8	Soliris	eculizumab	Alexion Pharma	2,590	2,843	+10%	12,389
9	Orencia	abatacept	Bristol-Myers Squibb	1,885	2,265	+20%	11,435
10	Tysabri	natalizumab	Biogen	1,886	1,964	+4%	12,074
Total Mab sales				70,915	81,850	+15%	564,249

Source: Company reports; Hardman & Co Life Sciences Research

Embracing new technology has been the key to success

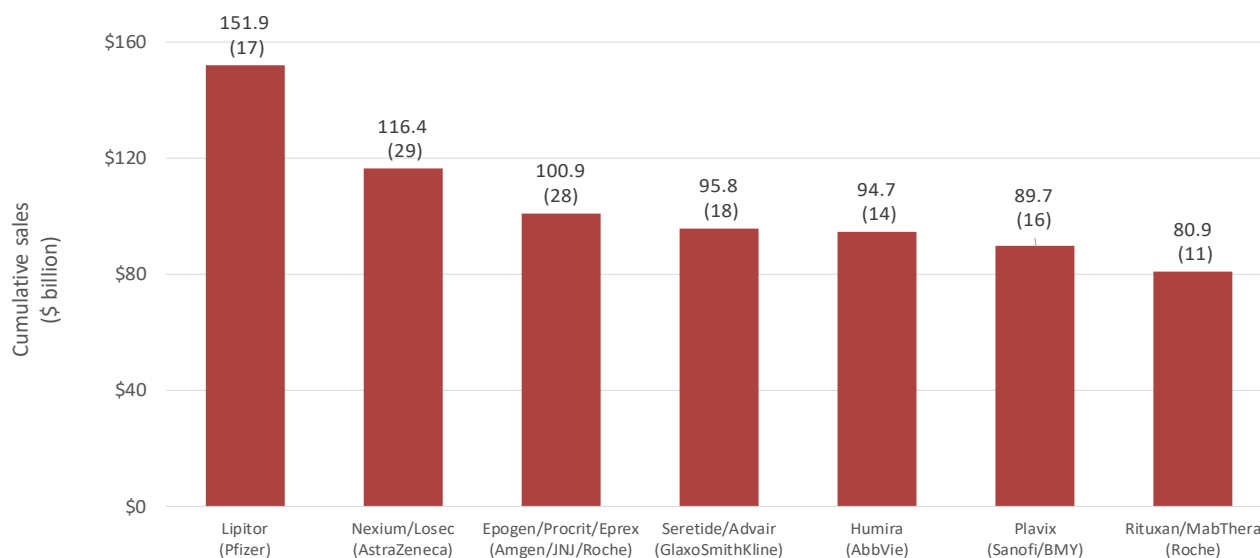
From the following table, it is clear that certain companies stand out, having embraced this new technology 20 years' ago. Roche was one of the first to buy-in to biotechnology through its innovative deal with Genentech. Novartis and Johnson & Johnson have also been active in bringing in new technologies. The rewards of these investments are demonstrable. Over the next few years, given recent approvals and anticipated approvals, we would expect to see Bristol-Myers Squibb and AstraZeneca featuring more in this list. The question for companies and investors alike is, therefore: what is the next technology that companies should be focusing on?

Cumulative sales – an alternative analysis

Three drugs have generated cumulative sales of >\$100bn

Although most analysis is done on sales made in an individual year and the growth that has been generated, the strength of our database allows us to look at the ex-factory sales in a slightly different way – cumulative sales since launch. We are not aware of any other analysts/statisticians that look at drug data this way – and it's great for pub quizzes! There are now three drugs that have achieved sales in excess of £100bn, with Lipitor (atorvastatin) way out in front at \$152bn over 17 years.

Top best-selling drugs on record



Number in brackets: full years of sales since drug launch

Source: Hardman & Co Life Sciences Research

About the authors

Dr Martin Hall

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Dr Martin Hall has been a pharmaceutical and healthcare analyst in the City for 30 years and joined Hardman & Co in 2013.

He studied Pharmacy (B.Pharm.Hons) at The London School of Pharmacy, followed by a Ph.D at the Institute of Psychiatry, London investigating the underlying mechanisms of Parkinson's Disease and schizophrenia. After post-doctoral experience at the Collège de France, Paris, and at the Parke-Davis (Warner Lambert) Research Centre in Cambridge, entered the City as a pharmaceutical/healthcare analyst in 1987, working mostly at UBS and HSBC, taking the strategic view that the sector should be viewed on a global basis. From 2004 until 2012, Martin worked at Eden Financial where he undertook bespoke research before developing a corporate finance franchise. This work has continued at Hardman & Co since 2013.

Dr Dorothea Hill

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Dr Dorothea Hill is relatively new to the City, joining the Life Sciences team at Hardman & Co in 2016.

Dorothea's expertise lies in next-generation sequencing, following her DPhil in molecular biology at the University of Oxford. Her academic research involved the use of genomics to understand the biology of bacterial pathogens in order to inform vaccine intervention. She was part of several public-private partnerships that involved biotech companies, patient charities, and Public Health England. Prior to her PhD, Dorothea worked for the Gates Foundation/Wellcome Trust-funded MenAfriCar Consortium, characterising the meningococcal epidemiology of countries of the African Meningitis Belt prior to MenAfriVac roll out. She is an author of nine peer-reviewed publications, and has a BA(Hons) in biological sciences from St Catherine's College, Oxford.

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Dr Gregoire Pave is also relatively new to the City, joining the Life Sciences team at Hardman & Co in 2016.

Greg has considerable experience in the field of drug discovery and development. After successfully gaining his PhD in medicinal chemistry in 2003, he obtained a post-doctoral position at Imperial College London, working on natural product synthesis. He then joined Cancer Research Technology, the development and commercial arm of Cancer Research UK in 2005 where he was involved in multiple oncology projects. Greg has broad experience in drug discovery/development projects from target identification/validation all the way through to clinical trials. He also gained valuable experiences in evaluating life science projects and their commercial opportunities. He played a role of reviewer in peer-review journals from the American Chemical Society. He is author of 14 scientific papers and owner of 4 patents, and holds the IMC and PRINCE2 qualifications.

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