

*'...discrepancies can result in a misleading evaluation of product R&D and the value of the company.'*

# editorial



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## Best-selling human medicines 2002–2004

► Reviewing medicines with multibillion dollar annual sales during the past three years reveals a steady increase in the number of such 'blockbuster' medicines. The emergence of Japanese companies as global players with innovative drugs, some generic and small companies linked with blockbuster drugs, the rise of biotechnology products and anticancer drugs and the success of 'me too' billion dollar drugs are other trends that become apparent from this analysis. The listing and sales figures for blockbuster medicines differ significantly if commercial reports are compared with company data. Such discrepancies can result in a misleading evaluation of product R&D and the value of the company.

### Sales forecast and projections

Forecasting and predicting the future markets and trends for pharmaceuticals and monitoring the actual market sales remain important tools for the industry to plan its growth, R&D and marketing strategy. Databases, including IMS, Datamonitor, Scrip, Prous, Reuters and IBM, and consultancy groups, such as Accenture, issue several commercial reports that provide a list of blockbuster drugs and their sales, the companies involved and market trends. The disadvantages associated with such reports are their high cost, the confidential nature of the data collection and evaluation, and the divergence of sales figures in comparison with company reports. Company websites and their annual and quarterly reports and presentations provide easy access to real sale data for best-selling products. However, some European and Japanese companies do not provide sales data for their best-selling products and do not follow the calendar year as their financial year.

There has been a gold rush of commercial highly priced Blockbuster Drug Reports and as many as 25 consultancy, advisory and data firms linked to the pharmaceutical industry have joined the bandwagon to generate hundreds of reports each year ([www.ims-global.com/insight/insight.htm](http://www.ims-global.com/insight/insight.htm); [www.datamonitor.com](http://www.datamonitor.com); [www.reutersbusinessinsight.com/content/rbhc0091t.pdf](http://www.reutersbusinessinsight.com/content/rbhc0091t.pdf)): the revenues, sales and profits generated from such reports are neither published nor reported. All commercial databases take shelter behind the safe harbour statement: 'models and methodologies for estimation of sales figures might give results that differ from actual results'. However, customers are still willing to pay US\$5000 for such data and projections. There is no independent comparative evaluation of past predictions and actual results or any oversight by regulators. In the era of Global Accounting Standards and the US Security and Exchange Commission (SEC) requirements, company reporting standards are well known

TABLE 1

**Best-selling pharmaceutical products 2002–2004**

Product Trade (Generic) name	Company	Sales figures for 2002 (US\$ billion)		Sales figures for 2003 (US\$ billion)		Sales figures for 2004 (US\$ billion)	
		Company	IMS	Company	IMS	Company	IMS
Lipitor (Atorvastatin)	Pfizer	7.90	8.60	9.23	10.3	10.86	12.00
Zocor (Simvastatin)	Merck	5.60	6.20	5.01	6.10	5.20	5.90
Plavix (Clopidogrel)	BMS and Sanofi-Aventis	3.10	NA	4.20	3.70	5.20	5.00
Advair (Fluticasone; Salmeterol)	GSK	2.00	NA	3.60	NA	4.50	4.70
Norvasc (Amlodipine)	Pfizer	3.80	4.00	4.33	4.50	4.46	4.80
Zyprexa (Olanzapine)	Eli-Lilly	3.60	4.00	4.27	4.80	4.42	4.80
Paxil (Paroxetine)	GSK	1.90	NA	3.00	3.90	3.90	3.90
Nexium (Esomeprazole)	AstraZeneca	1.97	NA	3.30	3.80	3.88	4.80
Zoloft (Sertraline)	Pfizer	2.74	NA	3.10	3.40	3.36	NA
Celebrex (Celecoxib)	Pfizer	3.00	NA	1.90	2.50	3.30	NA
Effexor (Venlafaxine)	Wyeth	2.00	NA	2.70	NA	3.30	3.70
Prevacid (Lansoprazole)	Takeda and Abbott	3.70	3.60	3.30	4.00	3.10	3.80
Diovan (Valsartan)	Novartis	1.66	NA	2.50	NA	3.10	NA
Fosamax (Alendronate)	Merck	2.20	NA	2.50	NA	3.10	NA
Risperdal (Risperidone)	J&J	2.10	NA	2.50	NA	3.00	NA

Global pharma market IMS US\$550 billion; global biotechnology market valued at US\$55 billion; global generic market US\$62 billion.

Table lists top 15 Medicines in 2004 with sales of over US\$3 billion.

Abbreviations: BMS, Bristol-Myers Squibb; GSK, GlaxoSmithKline; J&J, Johnson and Johnson; NA, not available.

and more reliable, whereas the methods used by commercial data houses remain confidential. All the sales projections for the same product for any year must be compared, irrespective of the methods used for data collection or source of data.

The Scrip annual review of the pharmaceutical industry and best-selling drugs, which is released at the beginning of each year, relies primarily on the data provided by IMS, but probably considers input from several other commercial databases. In 2004, the global pharmaceutical, biotechnology and generic markets were reported to be worth US\$550, US\$55 and US\$62 billion, respectively ([www.ims-global.com/insight/insight.htm](http://www.ims-global.com/insight/insight.htm)). In addition, based on their human drug sales and using predominantly IMS data, Sellers [1] identified several emerging trends in the top 50 pharmaceutical companies.

IMS does not claim that their data will match the in-house data of a pharmaceutical company and, for the same reason, do not recommend that data from the two sources are compared. IMS collects data on a country-by-country basis (from the majority of countries worldwide) from a sample of wholesalers and/or pharmacies and projects the data up to national level. There are some countries for which there is no IMS data, but these countries could be included in the company report. However, those excluded countries contribute little to the global market because >86% of the sales are in North America, Japan and Europe. IMS collects data from different points in the distribution process in different countries. Within IMS databases and systems, data are collected at wholesale, manufacturer or retail sales levels. Other factors that could contribute

to variations between company reports and IMS data include exchange rates, stockpiling of drugs, parallel imports, damages/returns bulk purchasing and discounting; these variables will also affect the company sales figures.

Inconsistencies are also observed with the best-selling medicinal products – different commercial reports rarely match sales figures provided by pharmaceutical companies. The high cost of commercial reports and projections for different years and various market segments have inhibited any public discussion of cost benefit and comparative analysis. For the purpose of this article, only data available in the public domain or on the websites of companies has been used.

### Comparative analysis

According to the sales figures provided by IMS ([www.ims-global.com/insight/insight.htm](http://www.ims-global.com/insight/insight.htm)), which are considered industry 'gold standard' and are widely used, of the best-selling human medicines for 2003 and 2004, only Lipitor (Atorvastatin; Pfizer), a lipid lowering drug, had sales in excess of US\$10 billion dollars (Table 1). However, examination of the sales figures released by Pfizer in the annual report ([www.pfizer.com/are/investors\\_reports/annual\\_2003/financial2003.pdf](http://www.pfizer.com/are/investors_reports/annual_2003/financial2003.pdf); [www.pfizer.com/annualreport/2004/financial/financial2004.pdf](http://www.pfizer.com/annualreport/2004/financial/financial2004.pdf)), produced in accordance with SEC regulations and globally accepted accounting standards, reveals that the figures quoted by IMS overestimate the sales of Lipitor in 2003 and 2004 by as much as US\$1 billion. Comparison of the sales figures released by companies producing medicines with sales in excess of US\$3 billion in 2004 (15 compounds in total) shows that

TABLE 2

**Best-selling biotechnology therapeutic proteins 2002–2004**

Product Trade (Generic) name	Company	Sales figures for 2002 (US\$ billion)	Sales figures for 2003 (US\$ billion)	Sales figures for 2004 (US\$ billion)
Epogen, Procrit, Eprex, Epogin, NeoRecormon and Aranesp ( $\alpha$ - and $\beta$ -erythropoietin)	Amgen, J&J, Roche, Kirin and Sankyo	8.60	10.30	11.80
PEG Intron, Pegasys, Avonex, Rebif and Betaseron ( $\alpha$ - and $\beta$ -interferon)	Schering Plough, Roche, Biogen IDEC, Serono, Schering AG and Chiron	5.60	5.20	6.80
Novulin, Humalin and Humalog (human insulin)	Novo Nordisk and Eli-Lilly	4.20	4.60	5.60
Neupogen and Neulasta (G-CSF)	Amgen, Roche and Schering	1.50	2.70	3.00
Rituxan (Rituximab)	Roche	1.10	2.20	2.80
Enbrel (Etanercept)	Amgen and Wyeth	0.80	1.30	2.60
Remicade (Infliximab)	J&J	1.30	1.70	2.10
Saizen, Humatrope, Protopin and Neutropin (human growth hormone)	Serono, Biogen IDEC, Roche, Novo Nordisk, Akzo Nobel and Eli-Lilly	1.20	1.60	1.80
Herceptin (Trastuzumab)	Roche	0.80	1.00	1.80
Synagis (Palivizumab)	MedImmune	0.67	0.85	0.95

In 2004, 197 marketed biotechnology products generated US\$55 billion. There are 100 biotechnology products in advanced stages of development and waiting for regulatory approvals and 800 are in clinical trials. The Table lists the top ten products that account for 69% of global biotechnology product sales.

the IMS figures differed by as much as US\$1 billion for two drugs [Lipitor and Nexium (Esomeprazole)] and >US\$0.5 billion for another four drugs in 2003 and two drugs in 2004 (Table 1). Differences in IMS values and company sales figures of less than US\$200 million were seen for only two drugs in the past two years [2].

### Biotechnology products

Biotechnology products or therapeutic proteins accounted for 10% of the global pharmaceutical market in 2004, and the ten products listed in Table 2 contributed 69% of the total biotechnology market sales for that period. There are 197 approved biotechnology products and a further 800 in development, including 100 products that are awaiting regulatory approval. Twenty brands of biotechnology products including individual brands of erythropoietin (EPO), interferon, granulocyte-colony-stimulating factor and insulin (Table 2) each had sales of over US\$1 billion in 2004 ([www.i-s-b.net/business/recombinant\\_f.htm](http://www.i-s-b.net/business/recombinant_f.htm)). Several companies market human growth hormone under different brand names, and thus these brands taken together make the bestsellers list (Table 2). If the sales figures for all brands of EPO are added together, EPO emerges as the best-selling human medicine and the only one with sales of over US\$11 billion. The IMS data give a figure of US\$11.4 billion compared with US\$11.8 billion reported by companies. Interferon and human insulin brands with sales of US\$6.8 billion and US\$5.6 billion, respectively, ranked as the third and fourth, respectively, best-selling products of the year (Tables 1,2).

Biologicals for the treatment of cancer and other life-threatening diseases also feature as some of the most expensive treatments. The average price of new biologics for cancer and rare diseases has increased from US\$20,000–25,000 to US\$100,000–280,000 per year.

The rise and importance of biologics has been discussed [3,4]. The blockbuster sales and high cost of biotechnology products and patent expiry of first generation products mean that biogenerics provide an attractive opportunity for established generic companies. Despite strong opposition from the biotechnology industry, regulatory authorities in the USA and Europe are expected to establish approval pathways for biogenerics or follow on biologicals in the next few years [3,4].

### Emerging trends in R&D

At present, of all the new chemical entities (NCEs), only ~30% are truly innovative. About 30–40% of the projects in 'big pharma' pipelines have been licensed in from other sources.

According to a report produced by Lehman Brothers in 2003 ([www.lehman.com/annual/archive/index.htm](http://www.lehman.com/annual/archive/index.htm)), the US patents on 35 drugs with global sales totalling more than US\$82 billion will expire in the next five years, resulting in the current US pharmaceutical market incurring losses of 25% (best case) to 40% (worst case) to generics. Reuters predicts patent expiry of US\$52 billion over the next four years, starting in 2004 ([www.reutersbusinessinsight.com/content/rbhc0091t.pdf](http://www.reutersbusinessinsight.com/content/rbhc0091t.pdf)).

There are no surprises in the therapeutic classes of blockbuster drugs (Tables 1,2). As in past years, lipid lowering, antiulcer, anticancer, antihypertensive, antidepressant, antipsychotic and antirheumatic drugs are the best-selling therapy classes: the top ten therapy classes comprise 33% of global pharmaceutical sales [1]. A Datamonitor report predicts that, by 2008, cardiovascular and central nervous system drugs will be the dominant classes and the number of oncology drugs in the blockbuster list will have increased ([www.datamonitor.com](http://www.datamonitor.com)). The blockbuster list highlights the success of the me too

NCE strategy of the R&D programmes of some companies – because even latecomers, such as the 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors and antiulcer proton pump inhibitors, can achieve blockbuster status [4].

The new trends point to increased R&D in oral antidiabetic peroxisome proliferator-activated receptor (PPAR) agonists, analgesic cyclooxygenase (COX)-2 inhibitors, antihypertensive angiotensin II receptor blockers, anticancer platinum, camptothecin, taxane, glivec and humanized monoclonal antibodies. With the introduction and successful launch of new statins, such as Crestor (Rosuvastatin) and Zetia (Ezetimibe), the market for lipid-lowering drugs will expand. The withdrawal of Vioxx (Rofecoxib), with sales of US\$2.5 billion in 2003, which had overtaken Celebrex (Celecoxib), with sales of US\$1.9 billion for the same time period, as the best-selling COX-2 inhibitor, will help celecoxib to regain its leadership status in the market ([www.fda.gov/cder/index.html](http://www.fda.gov/cder/index.html)). In 2004, celecoxib sales rose to US\$3.3 billion, as a result of patients previously prescribed rofecoxib being switched to treatment with celecoxib. The recent regulatory hearings, review and action by the FDA and European regulators adds 'black box' warning about increased cardiovascular risk of selective COX-2 inhibitors. Moreover, regulatory review of class toxicity, lack of long-term data with other COX-2 inhibitors [5] and concerns about increased cardiovascular risk will delay approvals of new inhibitors targeting COX-2, for example, Arcoxia (Etoricoxib) and Prexige (Lumiracoxib), thereby rendering celecoxib the analgesic of choice for high-risk patients [5]. The carcinogenicity and cardiotoxicity of PPAR agonists and new regulatory requirements implemented by the FDA will similarly delay approvals of new drugs with this activity ([www.fda.gov/cder/present/DIA2004/Elhage.ppt](http://www.fda.gov/cder/present/DIA2004/Elhage.ppt)), leaving only Actos (Pioglitazone) and Avandia (Rosiglitazone) to dominate the oral antidiabetic market.

The inclusion of Japanese companies in the list of those discovering and marketing blockbuster drugs started approximately ten years ago, and this trend has recently gained momentum. The current listing includes Takeda, Sankyo, Kirin, Yamanouchi, Fujisawa and Eisai, and signifies the maturation of Japanese companies as full-fledged global players with R&D capabilities. This is a shift from an earlier perception in the West of Japanese companies as being 'copy cat' producers of me too NCEs or new molecular entities, and as strong licensing or marketing partners. The change in emphasis from licensing to global development and direct marketing in the USA and European Union has contributed to the emergence and growth of Japanese companies. Additional mergers, such as Yamanouchi–Fujisawa and Daiichi–Sankyo, and consolidation could lead to the emergence of 2–3 large Japanese global players.

## Conclusions

Despite the demise of the blockbuster model proclaimed by pharmaceutical industry consultancy firms and gurus, the number of blockbuster drugs continues to increase year after year, regardless of the exits of several compounds as the result of patent expiry ([www.forbes.com/2003/10/08/cz\\_fmc\\_1008sf.html](http://www.forbes.com/2003/10/08/cz_fmc_1008sf.html)): in 2004, there were 79 chemical and molecular entities, which were marketed as 95 branded blockbuster drugs, including 20 branded biotechnology products. Similarly, the number of products with annual sales exceeding US\$3 billion increased from 13 in 2003 to 19 in 2004. The contribution of blockbuster drugs to profits is even greater than their 32% current share of the global pharmaceutical market.

The commercial reports and market forecast reports are popular, despite their high costs, and are used extensively by top management and executives of pharmaceutical, biotechnology, medical device and diagnostic companies, investment bankers, venture capitalists, fund managers, analysts and industry advisors. These reports allow executives to monitor performance of rival products and companies, and are considered when making decisions concerning the licensing of products, comarketing, takeovers, acquisitions and mergers and in the valuation of products, companies and R&D pipelines.

Reviewing the annual sales of top medicines from different sources can lead to misleading conclusions about the valuation of products and companies. A degree of management of commercial reports is required to minimize market manipulation and insider information. The listing of best-selling medicines, as reported by companies, show the increase of new blockbuster drugs, the global emergence of innovative Japanese companies and the shift of generic companies to new drug discovery.

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