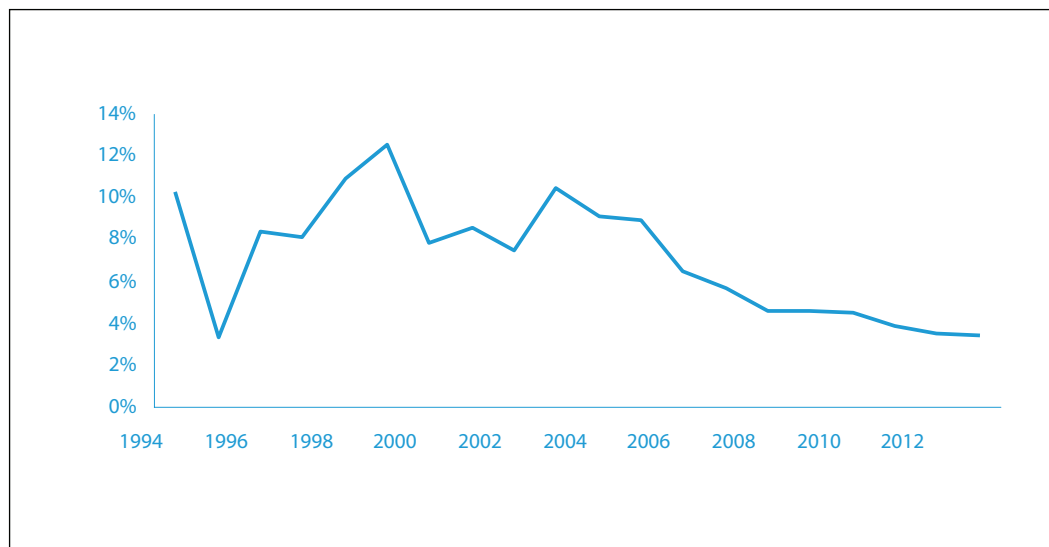


## Industry Overview

### Global ethical drug growth trends 1994-2013



Source: Wood Mackenzie

Wood Mackenzie estimates that the global pharmaceuticals market grew by 6.5% in 2006, with 6.4% growth in the US market and 6.7% growth outside the US. Cost containment still remains the key theme in major markets, although Wood Mackenzie believes that the overall impact of the introduction of the Medicare part D benefit in the US was positive on growth rates.

Although the introduction of Medicare part D represented a shift in payer type rather than a fundamental shift in the US market dynamics, the significant movement of dual eligible patients from Medicaid to Medicare likely unwound discounts to some degree, thus boosting market growth. Outside the US, market conditions were mixed. In the second-largest market, Japan, the biannual price cut was confirmed at an average of 6.7%, effective from 1 April 2006. In Europe, most companies reported tough market conditions in France and Germany as governments continued to implement measures to increase prescribing of generics and reduce prices of branded pharmaceuticals. Many companies continue to report positive growth trends in emerging markets, such as China and Brazil, although this growth does appear to be associated with increased volatility in some cases.

Looking forward, Wood Mackenzie estimates that the global pharmaceutical market will grow by 4.3% between 2006 and 2013, with the US growing at just below 4%. Centers for Medicare & Medicaid Services (CMS) is projecting an annual average growth rate to 2016 of 8.6% for the US retail market, driven by higher utilisation of expensive therapies, a levelling off in prescribing for generics and no further impact from Medicare Part D. Wood Mackenzie believes that the CMS projections underestimate the impact from generics, particularly in the CNS and cardiovascular sectors, in addition to pressure from continued cost-containment measures by payers and the potential for healthcare reforms under a Democratic president post-2008.

In Europe, we expect to see continued price pressure from government-led healthcare reforms on the brand-name pharmaceutical industry. As a counter to these measures, it will be interesting to evaluate the success of GlaxoSmithKline's potentially revolutionary value-based pricing model. In September 2006, GlaxoSmithKline announced that it had agreed with two European governments the ability to negotiate the prices of new medicines post-launch, based on the product's proven health benefits in the market place. The potential benefits of this scheme are significant, since the prolonged period of price negotiation which precedes launch would be eliminated and, post-launch, effective drugs could actually be subject to price increases.

### Issues regarding intellectual property

There were a number of developments in the sphere of intellectual property and patent protection in 2006, all of which are likely to have significant consequences for the future of the industry.

On 8 August 2006, Apotex launched its clopidogrel 75mg product, a copy of Bristol-Myers Squibb's Plavix which had US sales of \$3.8bn in 2005. Although the generic was removed from sale on 31 August 2006 following a court injunction, Apotex had managed to saturate the market with its product.

The Plavix issue commenced in January 2006, when Apotex's generic clopidogrel received final approval from the FDA following the expiry of the 30-month stay of approval. In March 2006, BMS and partner sanofi-aventis announced that a settlement had been reached with Apotex regarding upcoming litigation over the Plavix patents. In return for settling litigation, Apotex would be granted a license to launch its generic clopidogrel in September 2011, eight months before the patent expiry.

The settlement had to be approved by both the state attorney and the FTC. In June 2006, the settlement was re-negotiated with two key changes – BMS/sanofi-aventis waived its rights to triple damages and agreed not to seek an injunction for five days after any 'at risk' launch. In July 2006, the state attorney rejected the settlement and it was also stated that an FTC rejection was almost certain. Following the rejection of the settlement and the subsequent injunction preventing Apotex from selling its generic clopidogrel, the parties have resumed their litigation. The trial over the Plavix patents commenced on 22 January 2007, with a judgement expected in the second half of 2007.

While settling litigation by granting licences at the end of a product's life has clear attractions in terms of managing the patent expiry, it is clear that the regulatory authorities are taking an aggressive stance from a competition standpoint and that such deals are inherently risky. By attempting to settle, BMS and sanofi-aventis still opened the door to competition and restricted their rights to damages should they eventually prevail in the courts. Additionally, it seems unlikely that the US Plavix pricing model can be re-attained even if the patents are deemed to be valid.

Novartis is challenging the decision by the Indian Patent Office to decline issuance of a patent over Glivec, its oncology therapy. It is also challenging what it regards as additional hurdles put in place to prevent patents for innovative new medicines being granted in India. Novartis' stand is clearly not based on patient access, since 99% of patients in India receive Glivec with no charge, but is based on recognition of intellectual property by a developing country which has two distinct patient groups – the poor who cannot afford treatment and the middle class who can. Novartis makes it clear that receiving a patent on Glivec would have no impact on patient access to the drug in either India or any other developing nation and that over 40 countries, including China, have recognised the intellectual property surrounding Glivec. This is clearly an issue of significant importance, given the position of Indian pharmaceutical manufacturers both in their domestic market and overseas. It is also one which Novartis is having to manage from a public relations perspective – it received significant protests at its own shareholder meeting in March 2007.

### Developments in the field of 'biosimilars' or 'follow-on biologics'

Wood Mackenzie estimates that sales of biologic drugs, defined as those derived from any technical application using biological systems, living organisms or derivatives thereof (excluding vaccines), were \$70.4bn in 2006 with estimated market growth of 18.6%. The commercial opportunity offered by biologic drugs (both branded and unbranded), as well as the perennial question of affordability, is likely to keep the issue of biosimilars at the top of the agenda for the foreseeable future. We have seen two significant developments in the area of biosimilars during 2006.

Following the approval of Sandoz's Omnitrope (recombinant human growth hormone) by the European regulatory authorities in April 2006, the FDA finally approved Omnitrope in May 2006. The US approval followed a lengthy review process that culminated in Sandoz taking legal action forcing the FDA to make a decision. However, we do not believe that Omnitrope should be considered to be a precedent for a wave of biosimilar approvals in the US:

- Omnitrope is not a biosimilar – the FDA has termed Omnitrope a 'follow-on protein'.
- Omnitrope was approved via section 505(b)(2) of the Food, Drug, and Cosmetic Act (FDCA), a route which isn't available for the majority of biologic drugs which were approved under the Public Health Service Act (PHSA).
- Omnitrope is a relatively simple, well-characterised protein.

The Access to Life-Saving Medicine Act (re-filed February 2007) aims to create an abbreviated pathway for the approval of follow-on biologics in the US by amending the existing PHSA. The bill would empower the FDA to grant approval to biosimilars based on the ability to show comparability in terms of purity, safety and potency to the reference product. Specifically, the molecular structures of the biosimilar and reference product must be highly similar and have the same mechanism of action, route of administration, dosage form, strength and at least one common indication on the label.

The bill provides for marketing exclusivity to be granted to products that are deemed interchangeable with reference products, thus rewarding those companies prepared to undertake costly trials to support their products. The bill also contains provision to limit the duration of patent disputes and to set clear time-frames for FDA response times. The latter provision is controversial, since the eight-month timeframe for review would be quicker than a standard review for a new chemical entity and on a par with priority reviews, yet the only differentiating factors for these products against existing products would be price.

While the bill is clearly a further step towards creation of a biosimilars pathway in the US, it has several political hurdles to surpass and will be dependent on the FDA being able to create clear guidelines on the studies required to gain approval and provide adequate post-marketing safety surveillance. FDA Commissioner Andrew von Eschenbach stated in March 2007 that an end-point of similarity could be achieved, but that biosimilars would not be freely substitutable with the brand-name product.

Increasingly, brand-name pharmaceutical companies are turning to authorised generics as a means of dampening the impact of patent expiry in the US, by taking profit away from the generic manufacturer that has been awarded 180 days' exclusivity by the FDA. At present, there is nothing to stop a brand manufacturer from launching its own generic or granting a licence to a third party to launch an authorised generic either before the loss of exclusivity or during the 180-day exclusivity period.

Companies that introduced authorised generics in 2006 include AstraZeneca (Toprol XL, with Par), GlaxoSmithKline (Flonase, with Par) and Pfizer (Zoloft, via its subsidiary Greenstone).

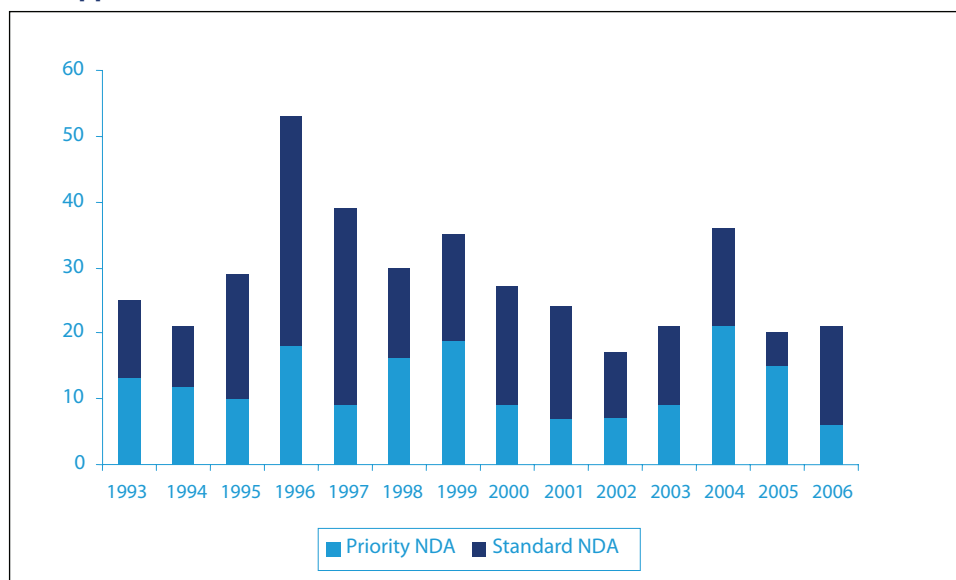
In the longer term, this tactic is clearly a disincentive to generic manufacturers, since the bulk of profits on a generic launch are made in the exclusivity period rather than the period after multiple players have entered the market. The practice of using authorised generics was investigated by the FTC in 2006, and hence it has come as little surprise that three Democratic senators, Rockefeller, Schumer and Leahy, have tabled the Fair Prescription Drug Competition Act of 2007, which aims to block marketing of such authorised generic drugs during the 180-day exclusivity period.

In a further development, on 17 January 2007, Senators Leahy and Kohl announced proposals to amend the Waxman-Hatch Act of 1984 to prohibit brand-name pharmaceutical companies from delaying the entrance of generic competition by making one-off payments to generic manufacturers to keep their products off the market. The announcement was made after publication of an FTC study which showed that half of the patent litigation settlements in 2006 between brand-name manufacturers and generic companies included payments in exchange for delayed entry of the generic launch. Prior to 2005, the FTC had successfully stopped such payments by bringing antitrust cases to trial, but after a challenge in the appeals court by Schering-Plough, which was ratified by the Supreme Court, such payments were deemed to be legal. This legislation is therefore seeking to amend the precedent set by the Schering-Plough case and would likely lead to increased litigation in the US courts as patent cases would be taken to conclusion.

### Product approvals in 2006

In the US, the number of approvals for new molecular entities in 2006 (21) was in line with 2005 (20) although the split between standard reviews (15) and priority reviews (6) was reversed.

### FDA approvals for NDAs 1993-2006



Source: CDER

The level of new product approvals in the US remains low relative to historic levels. This issue was the subject of a study by the US Government Accountability Office in November 2006. The report showed that while inflation-adjusted R&D expenditure rose by 147% between 1993 and 2004, the number of NDAs submitted to the FDA actually increased by only 38% over the same time period. Of more concern, was that NMEs rose only 7% in the same time-frame, but have actually been in decline since 1995. The report highlighted a number of factors for this fall in productivity, including limitations on scientific understanding, poor business decisions by pharmaceutical companies, uncertainty over regulatory standards and intellectual property protection.

New products that received approval during 2006 included oncology agents from Pfizer (Sutent), Merck (Zolinza) and Bristol-Myers Squibb (Sprycel). In other therapy areas, Genentech's Lucentis for wet AMD, Altana's ciclesonide for allergic rhinitis and Merck's Januvia for diabetes were all approved. Some notable compounds failed to clear US regulatory hurdles at the first attempt during 2006. The FDA extended user fee deadlines on Novartis' Galvus and Tekturna and Wyeth's Pristiq. Tekturna subsequently gained approval in March 2007, but further data were requested on Galvus, potentially delaying launch until 2009. sanofi-aventis' Acomplia was deemed approvable for weight loss and not approvable for smoking cessation and the FDA subsequently extended the user-fee deadline to July 2007.

In Europe, the EMEA reported receiving a record 78 marketing authorisations during 2006, of which 18 were for orphan drugs, nine for generics and three for biosimilars. Positive opinions for initial marketing authorisations were given on 51 compounds in 2006 by the EMEA, the highest number to date.

## Drug safety remains a key issue

Drug safety issues continued to dominate the US regulatory and political agenda during 2006.

The FDA, to which Andrew von Eschenbach was finally appointed commissioner on 13 December 2006, continued to be the object of criticism over its ability to manage post-marketing safety issues effectively.

In March 2006, the Government Accountability Office issued a report on drug safety entitled '*Improvement needed in FDA's post-market decision making and oversight process*'. The report criticised the structure of the FDA and, in particular, the relationship between the Office of New Drugs and the Office of Drug Safety.

In September 2006, the Institute of Medicine (IOM) published its report on drug safety, which concluded that:

- The credibility of the FDA and the pharmaceutical industry has been compromised by the safety issue
- Most stakeholders agree on the need for improvement in the system
- The drug safety system is impaired by the CDER organisational structure and an unclear and underpowered enforcement process
- The FDA and the pharmaceutical industry are inconsistent in demonstrating both accountability and transparency in communicating safety concerns to the public

The IOM made a number of specific recommendations in its report, namely that:

- Clinical trial registration should be mandatory
- The Office of New Drugs and the Office of Surveillance and Epidemiology should have joint authority for post-approval drug safety actions
- Post-approval scrutiny of drugs should match the way they are used in the general population
- CDER should improve its research capability to allow science-based regulatory decision making

The issue of clinical trial registration was also highlighted in 2006 by the World Health Organisation, which is promoting the International Clinical Trials Registry Platform initiative. The basic principles of the trial registry are that all interventional trials should be registered and that all data should be submitted before recruitment of the first participant. Not surprisingly, the industry is opposed to further disclosure of what it regards as commercially sensitive information and regards the proposals as stifling to innovation. In Wood Mackenzie's view, the debate on clinical trial transparency is set to continue for the medium term.

However, these actions did not prevent two pieces of legislation to address drug safety issues being tabled:

- Senators Grassley and Dodd proposed the formation of a separate drug safety unit within the FDA and greater emphasis on clinical trials registries via two bills, the Food and Drug Administration Safety Act of 2007 and the Fair Access to Clinical Trials (FACT) Act of 2007
- Senators Kennedy and Enzi re-introduced their Enhancing Drug Safety and Innovation Act, which had first been tabled in August 2006. The bill would '*require drug makers and the FDA to engage in better safety planning before a drug is approved for release to the public, while improving the FDA response to risks identified after a drug is on the market*'