# Whither generics? Why major restructuring lies ahead

Received (in revised form): 18th January, 2005

**Selena Class**
is Deputy Executive Editor of IMS Company Profiles, with extensive experience in company research and particular emphasis on generic manufacturers. Selena joined IMS in 1997 after a successful career as an editor at Elsevier Science.

**Abstract** Generic manufacturers have undergone some of the fastest growth in the pharmaceutical sector in recent years. But can their impressive growth rate be maintained post 2006–2007, when a number of blockbusters are due to lose exclusivity? Some of their major long-term challenges include the dearth of new blockbusters as branded pharma's pipeline dwindles; aggressive defence tactics such as the development of combination products and over the counter switching; authorised generic deals; the lack of an established approval path for biogenerics; and increasing competition from manufacturers in developing countries. For many, maintaining market share will require a transformation of their business practices. The successful organisations will be those that recognise the need for change early and start to plan their campaign of response accordingly. This paper outlines the issues they face and discusses some of the potential ramifications.

***Keywords:*** *generics; biogenerics; growth; competition; blockbuster; over the counter (OTC) switch*

Generic manufacturers have undergone some of the fastest growth in the pharmaceutical sector in recent years — six of the top ten fastest growing drug companies in 2003 were generics specialists, according to IMS Health's World Review. IMS data also show that sales of generic products grew three times as much as brands in 2003, and generic volumes exceeded 30 per cent in several major markets, including the USA, UK, Germany and Canada, fuelled by cost-conscious governments actively encouraging the use of generics as safe and cheap alternatives.

The short-term outlook continues to look promising for generics as cost-containment measures are strengthened in many developed countries — including the USA, where a number of pharmacy benefit managers are encouraging the use of unbranded products. There are also flourishing, and growing, markets for generics in newer areas, such as Russia and Latin America.

Selena Class
IMS Company Profiles
7 Harewood Avenue
London NW1 6JB
UK
E-mail: SClass@uk.imshealth.com

## Waiting for the big ones

While some branded company executives may look ahead with trepidation, many in the generics industry have their eyes firmly focused on 2006, when a number of blockbusters are due to lose exclusivity in the USA. Having made healthy profits since 2002 by selling copies of previous blockbusters, such as Prilosec/Losec (omeprazole), Claritin (loratadine) and Augmentin (amoxicillin/clavulanate), Table 1 highlights the opportunities awaiting generics manufacturers over the period 2005–2007. All of the brands each have US sales in excess of $1bn, while Zocor's (simvastatin) US revenues exceeded $4bn in 2003.

So, the future looks rosy for now. But post-2006/2007, when the blockbuster

**Table 1:** Major US patent expiries 2005–2007

| Brand | Compound | Indication | Owners |
|---|---|---|---|
| Zocor | Simvastatin | Hyperlipidaemia | Merck & Co |
| Norvasc | Amlodipine | Hypertension, angina | Pfizer |
| Zoloft | Sertraline | Depression | Pfizer |
| Pravachol | Pravastatin | Hyperlipidaemia | BMS, Sankyo |
| Zithromax | Azithromycin | Bacterial infections | Pfizer, Pliva |
| Ambien | Zolpidem | Insomnia | Sanofi–Aventis |
| Zofran | Ondansetron | Chemotherapy-induced nausea and vomiting | GSK |
| Zyrtec | Cetirizine | Allergic rhinitis | Pfizer, UCB |

BMS, Bristol–Myers Squibb; GSK, GlaxoSmithKline; UCB, Union Chimique Belge
Source: IMS LifeCycle Patent Focus

boom has dissipated, will the generics market as it stands today be sustainable? There are complex issues at play, which will call for a major rethink of established generics business practices. A significant shift in the required business model of the generics industry is predicted over the next 10–15 years. The need for change will be triggered not only by standard business drivers but also by a number of specific constraints that are currently challenging the status quo in this sector, as discussed below.

## Dwindling pipelines…

As the R&D companies know only too well, the innovative drug pipeline is not in a healthy state, with only 30 new chemical entities launched in 2003, according to IMS LifeCycle R&D Focus — the lowest number of new drugs for more than 20 years. Just as the brand firms must grapple with this now, so too will generics manufacturers in the future. Of course, every drug has to lose exclusivity eventually, and there are still plenty of blockbusters around today — led by Lipitor (atorvastatin), with global sales in excess of $10bn. But after 2007, there will not be the same number or quality of opportunities for generics.

Moreover, after being rocked by the effects of generics competition for iconic drugs like Prozac (fluoxetine), which lost 80 per cent of its sales within weeks, big pharma is beginning to get cannier about protecting its beloved blockbusters. Life cycle management is now one of the hottest issues in the brand industry, which is planning earlier, and thinking bigger in terms of maximising profits from their successful drugs. Some of the most popular tactics include:

- **Combination drugs:** Merck & Co began an alliance with Schering–Plough for its cholesterol absorption inhibitor Zetia (ezetimibe), which has been combined with Zocor to create Vytorin. Other examples include Pfizer's Caduet (Lipitor plus Norvasc) and Lilly's Symbyax (Prozac plus Zyprexa).
- **Once-a-day versions/ reformulations:** Many examples exist of companies prolonging the life spans of key compounds, while simultaneously increasing patient convenience and compliance, by utilising drug delivery technologies to provide once-daily dosing, rapid-melt tablets etc, including Adderall XR (mixed amphetamine salts), Cipro XR (ciprofloxacin) and Effexor XR (venlafaxine).
- **New indications:** Winning extended approvals can both boost sales and prolong a drug's life cycle, as some new indications may bring periods of exclusivity. This is a popular tactic in

the central nervous system arena, with antidepressants now being used for generalised anxiety disorder, panic, obsessive–compulsive disorder, pre-menstrual dysphoria disorder and social anxiety; trials have also been conducted in kleptomania.

- **Single-isomer/active metabolite versions:** These can be hugely successful, as demonstrated by Nexium (esomeprazole), the successor to Prilosec; it was the world's sixth best-selling pharmaceutical in the 12 months to September 2004. Similar products include Clarinex (desloratadine), the follow-up to Claritin (loratadine), and Lexapro/Cipralex (escitalopram), a second-generation version of Celexa/Cipramil (citalopram).

As the brand manufacturers promote these follow-on products as being safer, more convenient and cost-effective, generic firms will have to argue that their copies of the older compounds can provide better value for money while still offering maximum therapeutic benefit.

## The Over the counter switch route…

Many big pharmas are keen to switch threatened prescription drugs to over the counter (OTC) status, a strategy that was used successfully for the H2 receptor antagonists such as ranitidine, and in Europe and other markets for the non-sedating antihistamines. In the USA, these newer anti-allergy drugs remained prescription-only, until December 2002 — when Schering–Plough launched an OTC version of Claritin just one week before its US exclusivity expired; health insurers had long been lobbying for such a move.

In November 2002, generics manufacturer Andrx submitted a citizen's petition to the Food and Drugs Administration (FDA), trying to prevent the OTC switch for the 'Purple Pill' — AstraZeneca's Prilosec for heartburn and gastro-oesophageal reflux disease. This was unsuccessful, and in September 2003, AstraZeneca's partner Procter & Gamble (P&G) launched Prilosec OTC in the USA. It has proved highly successful: in late 2004, P&G was struggling to keep up with the demand. With much less fanfare, omeprazole also became available OTC in the UK in March 2004, when GlaxoSmithKline launched a version as Zanprol. GSK has also licensed OTC rights to Roche's obesity drug Xenical (orlistat), and has already launched Xenical as a non-prescription product in Australia and New Zealand, although OTC launches in the USA and Europe are probably still some way off. Andrx itself had a change of heart on the OTC market in January 2003, when it began an alliance with Perrigo, which will sell its generic loratadine range OTC.

In Europe, the biggest change to the OTC market came in July 2004, when Johnson & Johnson introduced Zocor Heart Pro 10 mg — the world's first OTC statin — in the UK under licence from Merck & Co (having bought out the latter's share of their 50:50 consumer health joint venture the previous February). The move, which is likely to be monitored closely by regulatory agencies around the world, could save the country's National Health Service significant sums of money: Zocor was the UK's top-selling branded prescription drug before losing exclusivity in May 2003. Through the royalties it receives, Zocor Heart Pro will also recoup some of Merck's losses to generics competition for Zocor in Europe. In the USA, the FDA rejected applications from Merck and Bristol–Myers Squibb to market Mevacor (lovastatin) and Pravachol (pravastatin) OTC in 2000. A new request for a Mevacor switch again received a negative

vote from an FDA advisory panel in January 2005, but Bristol–Myers Squibb said it would press ahead with its application for Pravachol. Mevacor lost US exclusivity in 2001, while Pravachol's is due to expire in 2006.

Although OTC switching is therefore growing in importance, as the Andrx/Perrigo deal suggests, it can also provide further markets for generics. As Brian Tempest, CEO of India's largest manufacturer, Ranbaxy, told IMS recently, it has a US subsidiary focused on the production of own-brand generic products for the large drugstore chains, such as Walgreen's. While OTC generics do provide another opportunity for manufacturers, however, the financial gains are not as attractive as those for prescription products, and thus further blockbuster switches are unlikely to be welcomed.

## Competition from big pharma...

As the pressure on R&D companies to increase shareholder value intensifies, fast-growing generics companies could prove to be a short-term target and fix for embattled CEOs. Several large firms are predicted to include generics companies on their list of purchases over the next few years. Some have already begun to recognise the value of owning their own generics arm and have taken steps towards vertical integration (for example, Novartis with Sandoz). While Pfizer has sold off a number of its European generics units, in the USA it launched its own generic version of blockbuster anticonvulsant Neurontin (gabapentin) through the Greenstone unit, following an 'at risk' launch of copies by Alpharma, and partner Teva. Forest also launched its own generic citalopram (licensed from Lundbeck) in October 2004.

## Authorised generic deals a mixed blessing...

Big pharma is also fighting back through so-called authorised generics, which effectively lessen the pain from the loss of exclusivity for their products, while dampening sales of the first generics competitor. They are actually not new, and occur on both sides of the Atlantic; for example, in March 2003, German manufacturer Hexal launched simvastatin in Germany six weeks before Zocord's (Zocor) patent expired through a deal with Merck & Co. In March 2004, however, Mylan won FDA approval and 180 days generic exclusivity for its copy of P&G's urinary tract infection treatment Macrobid (nitrofurantoin). P&G promptly signed an authorised generic deal with Watson for the product, which Mylan said would cut its expected revenue for the six-month period from $41m to $9m. The generics manufacturer has sued both the FDA and P&G, with CEO Robert Coury stating: 'The FDA by its actions has eliminated the 180-day exclusivity reward specifically provided to generic companies in the Hatch-Waxman Amendments. Congress could not have intended such a result'.

Of course, for every generics manufacturer that has its sales marred by an authorised generics deal, there is a rival that will benefit. Ranbaxy's CEO told IMS that he saw them as a 'business development opportunity'. While acknowledging that they could be a problem for larger rivals such as Teva, Brian Tempest said that Ranbaxy would be happy to act as an authorised generics partner for big pharma.

## Biogenerics delayed...

A frustrating issue for generics manufacturers is biogenerics — copies of the first biotechnology products. The worldwide biotech market is lucrative (see

**Table 2:** Top biotech products by global sales

| Brand name | Compound | Indication | Rank 2003 | Marketed by |
|---|---|---|---|---|
| Erypo/Procrit | Erythropoietin alpha | Anaemia | 6 | J&J |
| Epogen | Erythropoietin alpha | Anaemia | 15 | Amgen |
| Remicade | Infliximab | Crohn's, rheumatoid arthritis | 24 | J&J, Schering-Plough |
| Rituxan/MabThera | Rituximab | Non-Hodgkin's lymphoma | 37 | Biogen Idec, Genentech, Roche |
| Enbrel | Etanercept | RA, psoriasis, ankylosing spondylitis | 39 | Amgen, Wyeth |
| Neupogen | Filgrastim | Neutropaenia | 46 | Amgen, Roche |
| Aranesp | Darbopoietin alpha | Anaemia | 48 | Amgen |

J&J, Johnson & Johnson; RA, rheumatoid arthritis
Source: IMS World Review 2004

Table 2 below), accounts for a sizable percentage of products in the active pipeline and is expected to represent a growing proportion of the blockbuster market, yet no generic versions of biological products have been launched in any of the developed markets. This is not because the manufacturers are not ready, willing and able: the likes of Merckle, Sandoz and Teva have invested high levels of resources in the development of biogenerics. Unfortunately for them, however, regulatory agencies are understandably cautious and have found it difficult to reach decisions on the appropriate approval paths for biological copy products.

There were some signs of a resolution in 2004, with Australia approving Sandoz's Omnitrope (human growth hormone) in October. The FDA, which describes the products as 'follow-on proteins', held a public workshop into the issue in September 2004, but earlier in the month had informed Sandoz that it was unable to reach a decision on the approval of Omnitrope due to 'uncertainty regarding scientific and legal issues'. The European Commission has passed legislation for the approval of 'similar biological medicinal products', which is due to take effect in late 2005, and biogenerics applications can already be made to the European Medicines Agency (EMEA). Omnitrope received a positive opinion from the EC's advisory committee in June 2003, but was initially rejected by the EC, citing filing irregularities.

One of the main sticking points for biogenerics is bioequivalence, particularly as related to manufacturing processes. Although the first biotech products to be copied will be the simpler protein-based drugs, such as human growth hormone, insulin, erythropoietin and interferons (rather than monoclonal antibodies), the brand manufacturers argue that the manufacturing process of biologicals can have an impact on the finished drugs, and that biogenerics should therefore undergo full clinical testing before being approved; the generic drug makers argue that a protein is a protein, regardless of its method of production. If biogenerics, which already take longer to develop than small molecules, do require a significant amount of investment in clinical trials, they will be more like 'me-too' products, not offering the same price discounts as traditional generics, and probably requiring a higher level of promotion.

## Increasing competition...

While the use of generics in volume terms is growing at a healthy rate, they are lower margin products, and in 2003 accounted for less than 10 per cent of the global pharmaceutical market in sales terms at ex-manufacturer prices, according to IMS' MIDAS sales data. Generics manufacturers are now seeing intense competition in

well-developed generics markets, with new players from India and Eastern Europe, for example, now selling their generic versions in North America and Western Europe. As 180-day generic exclusivity is now often shared in the USA, companies can no longer rely on a lucrative honeymoon period for some of their products, and prices are driven down further and faster by multiple simultaneous generic launches.

Companies like Ranbaxy have the advantage of being vertically integrated — they make their own active ingredients, rather than relying on third-party suppliers — and years of experience of working in an extremely competitive domestic market. Others, such as Germany's Schwarz Pharma, can take advantage of earlier patent expiries in their domestic market to steal a march on their US competitors: after a protracted and complex legal fight, Schwarz ended up winning 180 days' generic exclusivity for generic omeprazole in the USA.

In Germany, one of the most mature markets for generics, Merckle's operating unit ratiopharm, has gone as far as running television advertising campaigns to raise consumer awareness of its products in a bid to drive market share. The German government has also been one of the most proactive on the cost-containment front, and even generics manufacturers suffered when it increased the compulsory manufacturer discount (for all prescription drugs not included in the reference price system) granted to statutory health insurance providers from 6 per cent in 2003 to 16 per cent in 2004. Products with the same active ingredient were also reference priced at the lowest third of the price range, although in general we still expect the generics market in Germany to see moderate growth, fuelled by the need to reference branded generics, the use of sales forces to promote products and the new reference price system which will mix brands and generics, the first five groups of which have been announced.

## Indians, then Chinese on their way…

The European and North American generics manufacturers are seeing increasing competition from Indian firms, with the larger companies such as Ranbaxy, Dr Reddy's and Cipla at the vanguard of an overseas expansion boom. A major impetus of this is India's adoption of the World Trade Organization's Trade-Related aspects of Intellectual Property rights (TRIPs) agreement from 1st January, 2005. This will see the introduction of some product patent protection in India, and will effectively call a halt to the practice of reverse engineering — the strategy that has allowed hundreds of generics manufacturers to flourish in India since product patents were effectively withdrawn in 1970.

Armed with their own active ingredients, FDA-approved facilities and a cheap, well-skilled workforce, the likes of Ranbaxy are well equipped to compete abroad; Ranbaxy was the third-largest filer of abbreviated new drug applications in the USA in 2003, according to CEO Brian Tempest, behind only Teva and Watson. Tempest expects a wave of Indian manufacturers to follow Ranbaxy into the US market; however, their biggest challenge as yet to successfully competing in the US market centres around distribution — many Indian manufacturers still have little or no infrastructure in North America and Europe, relying instead on distribution alliances with local partners. With the upheavals expected in their domestic market post-TRIPs, it is unclear whether many will have the resources to expand overseas — although this may ultimately be essential for their survival.

Looking further ahead, Ranbaxy's Tempest is not complacent, believing that Indian firms will have only 5–6 years to capitalise on their generics expertise on a global basis before they start to be undercut by Chinese producers, as the latter fall into line with accepted standards of good manufacturing practice.

## The options

There are a number of ways in which the generics industry can respond to the challenges. The simplest historically has been growth by acquisition. Several generics companies are already pursuing this path, changing from pure-play generics organisations to a combination of generic/R&D-style companies — such as Teva and Pliva — a model being copied by some of the newcomers to the international generics market, including Ranbaxy and Dr Reddy's. In particular, Teva's acquisition of Sicor positions Teva strategically very well to be able to capitalise on market developments, for example, in potential future biogenerics plus in differentiated technically complex formulations, both strategies that will increase the barriers for competitors.

Similarly, the recent suggestion that a 'polypill', based on six generic molecules, could have a significant impact on life expectancy and health spending, presents further opportunities for diversification. Companies choosing this route, however, would essentially be joining the path of an R&D-based company with all the knock-on implications — in terms of patent requirements, prerequisite clinical trial programmes, etc. Currently, few, if any, generics companies have a sufficient level of expertise and experience in this area, and they would need to reform themselves accordingly. The repackaging of old molecules in this way, and its reliance on a more detail-based marketing approach, calls for a new range of skills in sales force management. This would demand major changes in company structure — from a lean, effective organisation to a traditional pyramid-shaped company with multiple layers of management and a totally different cost base.

A number of generics manufacturers, including Apotex, Mylan and Teva, have diversified into the development of proprietary products. There have been some successes here, including Teva's multiple sclerosis therapy Copaxone (glatiramer acetate) and Ivax's respiratory franchise. Given the problems associated with developing new chemical entities, however, most companies are approaching this newer area with caution: the likes of Dr Reddy's and Ranbaxy have suffered a number of R&D pipeline setbacks, and in January 2005 Andrx said it would be divesting or seeking other strategic alternatives for its branded business.

## Implications

The bottom line is that generics houses will need to transform their business practices to maintain their share of the market. The successful organisations will be those that recognise the need for change early and start to plan their campaign of response accordingly. Those that fail to do so will be left behind as the continued existence and survival of the current dedicated generics company is increasingly called into question. In its place will be a more sophisticated organisation with a much larger number of representatives to market branded generics, more sophisticated sales and marketing expertise and the capabilities to undertake clinical trials; however, they will need to satisfy the FDA or EMEA if they wish to enter the lucrative North American and European markets.

One implication of all this change is a potentially bleak future for the small local generics companies. Even given the

potentially good growth rates, heavy discounting already shaves generics margins quite significantly. There are large concerns, too, that wholesalers will move into unbranded generics sourcing and supply. It is highly probable that the generics market of tomorrow will be dominated by a smaller number of larger companies. The US market is crucial — those European regional companies that have little or no US presence are potential acquisition candidates in the not too distant future.