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*As patents expire and innovation declines, the pharma/biotech industry must pursue aggressive strategies and adopt a fresh perspective to stay ahead.*

# Overcoming the Challenges in the Pharma/Biotech Industry

*by A.I. Graul and J.R. Prous*

*Summary*

In the face of patent expirations at a time of declining innovation across the industry, companies are restructuring their research and development operations and are pursuing an aggressive strategy of acquisitions, licensing deals and research collaborations to boost their drug pipelines. 

The pharma/biotech industry has suffered repeated setbacks in the last decade, with seemingly more bad news than good making the headlines, fewer new drugs reaching the market and bottom lines showing grimmer results. Several reasons for the industry slowdown have been put forward, as reviewed in the following sections, in order to put these challenges into perspective so that they may be surmounted.

## Increased generic competition

In 1984, the Drug Price Competition and Patent Term Restoration Act (originally known as the "Hatch-Waxman Act") was enacted, thereby establishing the modern system of generic drugs in the United States. This law expedites the availability of generic drugs and has popularized generic drug substitution. In the year 2004 alone, the U.S. FDA approved more than 400 generic products, a record number for that agency. In countries outside the United States, especially in Europe, sales of generic drugs have also increased significantly in recent years.

Over the last two decades, pharmaceutical research-based companies have grappled with the problem of increased generic competition. In the long run, however, companies may be stimulated to develop new products to offset the plunging sales of those products whose patents have expired or are near to expiration. This is already the case in the United States, where more than 50% of medications used are generics,[1] and at the same time, where more new drugs are developed than any other country in the world.

One frequently cited example of a popular generic is the diabetes drug metformin (marketed by Bristol-Myers Squibb as *Glucophage®*), which lost patent protection in January 2001. The drug, which racked up sales of USD 1.7 billion in the year 2005, is one of the largest-volume synthetic prescription drugs on the market worldwide, due to the fact that it treats a chronic disease and is administered as a comparatively large dose. This drug is considered to be a valuable generic opportunity, and is reportedly available from more than 40 suppliers worldwide at a significantly lower price than the brand product.[2]

It is expected that by the year 2012, drugs worth more than USD 50 billion in sales will go generic (Table I). According to *CNNMoney.com*, the outlook is even grimmer: in April 2006, this source reported that blockbuster drugs worth more than USD 100 billion would lose patent exclusivity in the next 5 years. The shock waves from the loss of patent protection may be even more widely noted: experience has demonstrated that when one drug in a class—such as simvastatin in the statin class—goes generic, other drugs in the same class may also suffer lost sales. Patent pro-

tection for *Zocor*® (simvastatin), Merck & Co.'s best-selling product in the U.S. market, lapsed last summer, and generic versions of *Zocor* pushed Merck's sales of the branded drug down by 65%, to USD 379 million, in the last quarter of 2006 as compared with the same period in 2005. The company is already struggling overseas with the competition presented by generic forms of *Fosamax*®, its osteoporosis drug, which will go generic in the United States as well in 2007. The company is hoping that sales of newer products, including *Gardasil*® and *Januvia*™, will help to make up for these losses.

A more recent development in the drug industry has been the loss of patent protection for biologics, biopharmaceuticals and biotechnology drugs. Generic versions of these products—known as biosimilars—are now being developed. The first two such products were approved last year in the European Union: Sandoz's *Omnitrope*® and Biopartners' *Valtropin*®, both generic versions of Pfizer's *Genotropin*® (somatropin [rDNA]). This was enabled by the EMEA's adoption, in late 2005, of guidelines regulating the development and marketing authorization of this type of product. European regulators expect to soon begin receiving applications for biosimilar versions of insulin, erythropoietin (EPO) and granulocyte-colony stimulating factor (G-CSF), among others. Biosimilar medicines are also authorized for sale in Australia and some countries of Asia and Latin America.

In the United States, *Omnitrope* received U.S. approval in May 2006 as the first "follow-on version" of a previously approved recombinant biotechnology drug. The FDA declined, however, to classify the drug as a biogeneric (as these drugs are commonly called in the United States) and said that its approval did not set a precedent for other biological medicines in that country. According to the FDA, the drug's designation as a follow-on product indicates that its similarity to previously approved human growth hormones (in this case, *Genotropin*) allowed consideration of the safety and efficacy data for the latter as part of the approval process. However, the FDA stressed that *Omnitrope* "is not therapeutically equivalent to (and therefore substitutable for) any other approved human growth hormone products." This was not even the first time that the agency had approved a follow-on version of a protein therapeutic: other follow-on protein products previously approved under section 505 of the Food, Drug and Cosmetic Act include *GlucaGen* (glucagon recombinant for injection), *Hylenex* (hyaluronidase recombinant human), *Hydase* and *Amphadase* (hyaluronidase) and *Fortical* (calcitonin salmon recombinant) nasal spray.[4] The widespread approval of biogenerics in the United States cannot occur until appropriate legislation is in place. This is clearly a decision that will have important financial repercussions in the industry. According to the U.S. Generic Pharmaceutical Association (GPhA), biopharmaceuticals worth more than USD 10 billion will come off patent over the next 5 years.

Table I presents selected blockbuster drugs for which U.S. patent protection will soon lapse. A list of selected companies involved in generics is presented in Table II.

The approval in January 2006 of Medicare Part D in the United States may provide some impetus to both generic and prescription pharmaceutical drug companies in that country. Part D is a new, first-time Medicare prescription drug benefit that provides

**TABLE I. SELECTED BLOCKBUSTER DRUGS LOSING U.S. PATENT PROTECTION DURING 2007–2012**

| PRODUCT | COMPANY | PATENT EXP. DATE* | 2006 SALES (IN USD)** |
|---|---|---|---|
| Alendronate (*Fosamax*) | Merck & Co. | August 2007 | $3.1 billion |
| Cetirizine (*Zyrtec*) | UCB | June 2007 | $2.5 billion (estimated) |
| Interferon beta-1b (*Betaseron*) | Berlex/Bayer Schering Pharma | July 2007 | $1.2 billion (estimated) |
| Risperidone (*Risperdal*) | Johnson & Johnson | December 2007 | $4.2 billion |
| Lansoprazole (*Prevacid*) | Takeda | May 2009 | $4 billion |
| Atorvastatin (*Lipitor*) | Pfizer | September 2009 | $13.7 billion |
| Docetaxel (*Taxotere*) | sanofi-aventis | May 2010 | $2.2 billion |
| Donepezil (*Aricept*) | Eisai | November 2010 | $2.1 billion |
| Pioglitazone (*Actos*) | Takeda | January 2011 | $2.6 billion |
| Clopidogrel (*Plavix*) | Bristol-Myers Squibb/sanofi-aventis | November 2011 | $6 billion |
| Enoxaparin (*Lovenox*) | sanofi-aventis | February 2012 | $3 billion |
| Sildenafil (*Viagra*) | Pfizer | March 2012 | $1.7 billion |
| Tolterodine (*Detrol/LA*) | Pfizer | March 2012 | $1.1 billion |

*__Source:__ U.S. Patent and Trademark Office (http://www.uspto.gov/web/offices/pac/dapp/opla/term/156.html, consulted December 13, 2006).
**__Source:__ *Integrity*®, based on company-reported sales figures.

**TABLE II. PARTIAL LIST OF COMPANIES INVOLVED IN GENERICS**

| |
|---|
| Actavis |
| Alpharma |
| Amphastar Pharmaceuticals |
| Aspen Pharmacare |
| Apotex |
| Barr Laboratories |
| Cangene |
| Cipla |
| Dr. Reddy's Laboratories |
| EGIS |
| Gedeon Richter |
| King Pharmaceuticals |
| Lannett |
| Merck Generics |
| Mylan Laboratories |
| Nichi-Iko |
| Par Pharmaceuticals |
| Perrigo |
| Ranbaxy |
| Ratiopharm |
| Sandoz |
| Sawai |
| Sicor |
| Stada Arzneimittel |
| Teva |
| Towa Pharmaceutical |
| Watson |
| Winthrop |
| Wockhardt |
| Zydus Cadilla |

increased access to prescription medications for senior citizens and the disabled. Medicare has provided hospital, physician, medical equipment and other health services to beneficiaries for more than 40 years, but until now did not cover prescription medications. The program has also been expanded to cover poor and low-income beneficiaries, as well as increased preventive care. All of these modifications are expected to have positive repercussions throughout the pharmaceutical industry, but especially for generic drug manufacturers.

## R&D failures

The all-too-frequent failure of drugs in an advanced stage of clinical testing incurs a significant loss of time and money for pharmaceutical companies. According to one analysis, more than 40% of drugs that enter phase III clinical testing are discontinued due to problems related to efficacy, safety or both. Furthermore, phase III trials are the most costly stage of development, accounting for up to 70% of the total cost of developing a drug.[5]

Some factors have been found to be associated with a higher failure rate than normal. Not surprisingly, drugs with a novel mechanism of action fail more frequently in clinical testing than those with a tried-and-true mechanism. Similarly, drugs for difficult-to-treat indications such as stroke and other CNS disorders as well as cancer drugs are associated with a higher failure rate, often because animal models of these human diseases are imprecise and poorly reflect the human condition.[5]

All too frequently, however, drugs are dropped from development for reasons that are neither scientific nor technical in nature. According to one estimate, as many as 25% of the drugs that are eliminated from company pipelines are discarded due to managerial decisions regarding shifting priorities, marketing reassessment or loss of management interest when development takes longer than expected.[6] On the contrary and no less importantly, however, many drugs are pushed through clinical development in spite of inconclusive results because companies are reluctant to admit failure, for both emotional and financial reasons. This reluctance ultimately backfires, with drugs eventually being withdrawn from the pipeline at a later stage, when significantly more resources have been poured into their development.

Some of the more notable examples of trial discontinuations that made the news during 2006 include the following:

- In December 2006 Pfizer halted all clinical trials of the cholesterol ester transfer protein (CETP) inhibitor torcetrapib, which had been the most advanced product in this promising new class of atherosclerosis therapeutics, in interests of patient safety. The decision was made based on recommendations by an independent Data Safety Monitoring Board (DSMB), which was monitoring the ILLUMINATE morbidity and mortality study of torcetrapib (in combination with atorvastatin). The DSMB noted a significant increase in mortality (82 deaths vs. 51 in the control group) and cardiovascular events (a 3- to 4-mmHg increase in systolic blood pressure) in patients receiving the combination as compared with those receiving atorvastatin alone. The company elected to terminate the ILLUMINATE study as well as the development program for this compound. Pfizer claimed that the new information from the trial was totally unexpected, although a previous report from a phase II trial had in fact already indicated systolic blood pressure increases with the drug combination.[7] Pfizer's shares took a dive upon disclosure of the news, dropping 11% on the day of the announcement. The company had invested USD 800 million in the clinical development of torcetrapib, expecting the drug to be its next blockbuster.

- In October AstraZeneca discontinued development of NXY-059 (disufenton sodium) in acute ischemic stroke after NXY-059 showed lack of efficacy in the SAINT II (Stroke Acute Ischemic NXY-059 Treatment) trial. In contrast to previous phase III results, which had been described as promising,[8] the new results showed that NXY-059 did not meet its primary outcome of a statistically significant reduction in stroke-related disability, as assessed by the modified Rankin Scale (mRS) compared to placebo. Subgroup analyses, including time to treatment, did not demonstrate a

treatment benefit. In addition, NXY-059 did not cause a statistically significant improvement in neurological status versus placebo on the National Institutes of Health Stroke Scale. There was no evidence of NXY-059 lowering the incidence of symptomatic intracranial hemorrhage when administered with rt-PA. Mortality and the incidence and profile of adverse events in patients receiving NXY-059 were similar to placebo. Renovis appears to have opted to continue development of the product for the treatment of hemorrhagic stroke. Both companies suffered serious losses upon announcement of the negative results: AstraZeneca shared dropped by 7.5% and those of Renovis by a whopping 75%.[5]

- In the Spring of 2006 news channels were filled with the horrifying story of a phase I trial that went tragically wrong. Of eight healthy volunteers who participated in the first clinical experience with TeGenero's TGN-1412, the six who received the experimental drug suffered catastrophic multisystem failure as a result of a "cytokine storm." The drug, a humanized monoclonal antibody to the CD28 T-cell surface receptor, induced a systemic inflammatory response within minutes of administration characterized by headache, myalgia, nausea, diarrhea, erythema vasodilatation and hypotension. Within 12–16 hours of dosing, subjects manifested lung injury, renal failure and disseminated intravascular coagulation, and two of these progressed to prolonged cardiovascular shock and acute respiratory distress syndrome. Fortunately, all six volunteers survived. The two volunteers who were given placebo showed none of these effects.[9] In July 2006, TeGenero filed insolvency proceedings.

The development of several other drugs was discontinued during the year just past, as reported in *DailyDrugNews.com* and summarized in Table III.

An even more costly "mistake" is the approval and marketing of drugs that must later be withdrawn from the market, most often due to safety problems that were not detected during clinical testing. Several products were withdrawn last year from markets worldwide, including AstraZeneca's anticoagulant *Exanta*™ (ximelagatran), announced in February 2006. The company made the decision to withdraw the product and discontinue all further development upon learning of serious side effects in ongoing clinical studies. Results obtained in the EXTEND clinical trial, which was

**TABLE III. SELECTED PRODUCTS DISCONTINUED FROM CLINICAL DEVELOPMENT IN 2006**

| PRODUCT | COMPANY | STATUS WHEN DROPPED | REASON |
|---|---|---|---|
| Fenofibrate/metformin (*Synordia*) | Solvay | Preregistered | Company unable to respond to need for additional information in the specified time frame |
| Muraglitazar | Bristol-Myers Squibb | Preregistered | Need for additional trials to obtain approval; competition from other products |
| Rubitecan | SuperGen | Preregistered | MAA withdrawn pending receipt of results of an ongoing phase II trial |
| Disufenton sodium (acute ischemic stroke indication) | AstraZeneca | Phase III | Lack of efficacy |
| Lonidamine | Threshold Pharmaceuticals | Phase III | Lack of efficacy; adverse effects |
| Temsirolimus (breast cancer indication) | Wyeth | Phase III | Low probability of efficacy, as determined by DSMB |
| Tesaglitazar | AstraZeneca | Phase III | Lack of benefit over existing therapies |
| Torcetrapib | Pfizer | Phase III | Safety concerns |
| GR-270773 | GlaxoSmithKline | Phase II/III | Unfavorable benefit/risk profile |
| Troxacitabine (AML indication) | SGX Pharmaceuticals | Phase II/III | Low probability of efficacy, as determined by DSMB |
| AD-452 | Sosei | Phase IIb | Lack of efficacy |
| Dexelvucitabine | Incyte | Phase IIb | Adverse effects |
| rEV-131 | Evotec | Phase IIb | Lack of efficacy |
| Balicatib | Novartis | Phase II | Reason undisclosed |
| Brecanavir | GlaxoSmithKline | Phase II | Formulation problems |

*Cont.*

**TABLE III CONT. SELECTED PRODUCTS DISCONTINUED FROM CLINICAL DEVELOPMENT IN 2006**

| PRODUCT | COMPANY | STATUS WHEN DROPPED | REASON |
|---|---|---|---|
| CRx-140 | CombinatoRx | Phase II | Lack of efficacy |
| DITPA | Titan | Phase II | Reallocation of resources |
| Emapunil | Dainippon Sumitomo Pharma/Novartis | Phase II | Development plan under review |
| Ethyl pyruvate | Critical Therapeutics | Phase II | Stability issues |
| FK-962 | Astellas | Phase II | Lack of efficacy |
| Male hormonal contraceptive | Schering AG/Organon | Phase II | Poor product acceptability |
| Manitimus | Astellas | Phase II | Lack of benefit over existing therapies |
| MK-0354 | Merck & Co. | Phase II | Reason undisclosed |
| ONO-6126 | Ono | Phase II | Lack of efficacy |
| Pranlukast (COPD indication) | Ono | Phase II | Lack of efficacy |
| Rivenprost | Ono | Phase II | Lack of efficacy |
| TAK-128 | Takeda/Mitsubishi Pharma | Phase II | Lack of efficacy |
| TAK-715 | Takeda | Phase II | Did not meet development criteria |
| CER-227185 | Cerep | Phase I/II | Adverse effects; narrow therapeutic window |
| EVT-301 | Evotec | Phase I | Adverse effects |
| ONO-4127.Na | Ono | Phase I | Poor oral absorption |
| TGN-1412 | TeGenero | Phase I | Serious adverse effects |

**Source:** *Integrity®* and *DailyDrugNews.com*.

evaluating a longer treatment period than that approved in Germany in 2004, indicated a potential risk of severe liver injury, with an observation of rapid onset of signs and symptoms in the weeks following the end of the 35-day treatment period. The company elected to suspend marketing of the product in Germany and to withdraw regulatory applications in other countries worldwide. Although the company said in its press release announcing the action that this side effect had not been previously observed, an FDA advisory committee had in fact recommended against approval of the drug in the United States in September 2004, citing as one reason the observation of an increased incidence of severe liver injury among patients taking the drug.

Postmarketing changes in recommended dosages are another less well-known but no less common occurrence that also have significant effects on patients, drug companies and regulatory agencies. These dosage adjustments, both increases and reductions, could be avoided through more rigorous dosage optimization studies prior to phase III testing and regulatory approval.[10] These same strategies could also be applied to help prevent the occurrence of market withdrawals.

On a related note, the trend in recent years to initiate marketing of new drugs on a massive scale has had an unfortunate downside: by the time unexpected and serious side effects are encountered in postmarketing and pharmacovigilance studies (which, of themselves, are hindered and made more difficult by the massive marketing campaigns accompanying new launches), millions of drug exposures have already taken place. This occurrence was much less common in the past, when the medical community was more cautious about using new medicines and companies built up their franchises more gradually.[6]

## R&D expenditures

During the 1980s pharmaceutical R&D expenditures grew steadily. According to the Pharmaceutical Research and Manufacturers of American (PhRMA), in the United States, investment increased from USD 2 billion in 1980 to USD 8.4 billion in 1990.[11]

Current figures are even more astounding. According to a report released in November 2006 by the U.S. Government Accountability Office, industry-reported annual R&D expenses (after adjustment for inflation) rose from USD 16 billion in 1993 to almost USD 40 billion in 2004, an increase of 147%.[12] In 2005, the entire biopharmaceutical industry of the United States (both PhRMA members and nonmembers) invested more than USD 51 billion in R&D.[11] This investment is greater than the total annual budget of the National Institutes of Health, reported at USD 28 billion.[6,11] The number of new drug applications (NDAs) submitted to the FDA over the same time period did not reflect this investment, however, with an increase of only 7% in the number

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