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Biosimilars Come to the Fore

Generic Drugs' Future Far From Ordinary

by Amy E. Buttell

It doesn't take a crystal ball to realize that the long-term prospects are bright for the generic drug industry. A confluence of factors — numerous branded-drug patent expirations, the prospect of generic biotechnology drugs and a favorable regulatory environment — is driving up valuations and presenting some intriguing opportunities for investors during the next three to five years.

Patents on nearly 20 major branded drugs are scheduled to expire in the next three years *(see table, page 23)*, so generic drug companies are stampeding to the U.S. Food and Drug Administration to file applications to bring the first generic version of each branded drug to market. For companies filing early and often, such exclusivity brings a six-month window to sell the drug with no or limited competition, fattening revenues.

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Beyond the next couple of years, generic versions of biotechnology drugs are expected to reach the market, although there's a lot of uncertainty about legal, regulatory and safety issues. These generic biologics — or biosimilars, as they are also known — aren't the slam-dunk for generic drug companies that traditional compound-based drugs are, so there will also be manufacturing issues and perhaps the requirement of limited clinical trials.

On the regulatory front, the Obama administration is pushing for more generic competition and is in favor of generic biologics, mainly because of their cost-saving potential. With the appointment of new directors and assistant directors of the FDA pending, as well as a significant increase in the agency's budget, regulation will likely increase.

In general, the drug business is fairly recession-resistant and the generic portion of the business is even better positioned to ride out an economic downturn, says George Haley, Ph.D., director of the Center for International Industry Competitiveness at the University of New Haven's College of Business. "Generics, in particular, should outperform the balance of the industry, simply because you will find doctors more willing to permit the use of generics because their patients are, in many instances, losing their jobs and medical insurance coverage," he says.

Patent Expirations

In both the near and long term, branded-drug patent expirations will be a boon to the bottom lines of generic drug companies. Major blockbusters such as Pfizer's cholesterol drug Lipitor, Eli Lilly's antipsychotic Zyprexa and the sanofi-aventis/Bristol-Myers Squibb medication Plavix are all coming off patent.

"Billions and billions of dollars of branded pharmaceuticals are losing exclusivity over the next four years," says Damian Conover, a drug company analyst with Morningstar. "The generic companies who are the first to launch on the generic product get a six-month window of exclusivity pricing alongside the branded drug, and that is a huge return. I think this factor will really drive revenues for the more traditional generic forms over the next two to four years."

FDA rules stipulate that branded-drug companies have the exclusive right to market their drugs for the length of their patent. Patents typically run 20 years, but at least a third or sometimes half of that time is eaten up in the drug approval process. Because branded-drug franchises are so valuable, pharmaceutical companies typically vigorously defend their patents through a variety of means, including lawsuits and even paying millions of dollars to potential generic competitors to postpone the introduction of generic versions.

The continuing drive by governments and private payers to cut costs is also fueling growth in generic drugs, as these payers pressure providers and consumers to use cheaper medications. "We're seeing a lot of countries with governments focused on trying to cut health care costs, and generics are obviously looked on as a top priority in terms of achieving that objective," says Barath Shankar, industry analyst, pharmaceuticals and biotechnology, at Frost & Sullivan. "A lot of underdeveloped nations are seeing interest from Western countries and nonprofit groups that want to cut the rate of infectious diseases and see generics playing a big role there."

Generic Biologics

A huge potential area of growth for generic and branded-drug companies, both in the United States and abroad, are generic biotechnology drugs, also known as generic biologics or biosimilars. Because the biotechnology industry is relatively new compared with the branded-pharmaceutical industry, patent expirations and generic drug competition hasn't been an issue for biotech com-

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panies. But as patents expire and governments begin to regulate this emerging industry, it's fast coming to the fore.

Europe has already begun to construct a framework for approving generic biologics through its regional regulator, the European Medicines Agency. Legislation has been introduced in Congress to provide a similar pathway for approval and regulation of generic biologics. Now that this legislation has the backing of the Obama administration, it's much more likely to pass.

Still, major issues are involved in creating a developmental and regulatory system to regulate generic biologics. These include:

- **Safety:** With many manufacturing facilities for generics located in less-developed nations, safety is a major issue for any generic drugs. This is especially the case for generic biologics because the manufacturing process is much more complex than for traditional drugs derived from chemical compounds. "Generic companies that want to develop biosimilars need to gain the technical skills necessary to undertake production and get the regulatory approvals necessary in both the United States and Europe," Haley says.
- **Legal:** Biotechnology companies frequently seek to patent their manufacturing and development processes. This potentially places more barriers in the way of generic companies seeking to make biosimilars.
- **Regulatory:** In the United States, the FDA is already understaffed as applications for traditional generics pile up. Even after legislation is passed and signed by the president, rules and regulations must be developed to provide a framework for approval of biosimilars. There's a good chance generic companies producing these medications might have to participate in limited clinical trials of generic biologics to prove they're similar enough to the biotech drugs they're seeking to emulate.

Major Branded-Drug Expirations

Drug name	Drug type	Company	Patent exp. date
Crestor	Cholesterol	AstraZeneca	2012
Symbicort	Asthma	AstraZeneca	2012
Seroquel	Antipsychotic	AstraZeneca	2011
Zyprexa	Antipsychotic	Eli Lilly & Co.	2011
Actos	Type II diabetes	Eli Lilly & Co.	2011
Lexapro	Antidepressant	Forest Laboratories	2012
Advair	Asthma	GlaxoSmithKline	2010
Avandia	Diabetes	GlaxoSmithKline	2012
Levaquin	Antibiotic	Johnson & Johnson	2010
Singulair	Asthma	Merck	2012
Cozaar	Hypertension	Merck	2010
Zometa	Cancer	Novartis	2012
Diovan	Hypertension	Novartis	2012
Lipitor	Cholesterol	Pfizer	2011
Aricept	Alzheimer's	Pfizer	2010
Xalatan	Glaucoma	Pfizer	2011
Aprovel	High blood pressure	sanofi-aventis/ Bristol-Myers Squibb	2011
Plavix	Anticoagulent	sanofi-aventis/ Bristol-Myers Squibb	2011

Source: Company reports, Morningstar

Because of all these constraints, Conover estimates that actual sales and marketing of generic biologics to consumers is at least two, and possibly three or four years, away. In addition, the issue of how long it will take for biosimilars to reach the market is depressing the valuations of biotech company stocks, says Maik Klasen, Ph.D., senior director of health care consulting for Frost & Sullivan. This is because these companies previously were immune from generic competition.

Regulatory Roadblocks

Although the FDA is due to receive a large budget increase in the Obama administration's budget, it will take time for the federal funds to be put to work, even if the budget isn't trimmed down by Congress. Generic and branded-drug applications are backed up, and the FDA is woefully understaffed in terms of inspecting drug manufacturing facilities both here and abroad.

This has troubling implications for drug safety. More and more drugs are produced overseas, where it's harder for the FDA to inspect facilities because of language barriers and travel issues. Arun Ravi, health care consultant with Frost & Sullivan, sees potential for the FDA to collaborate more with the European Medicines Agency, extending its reach.

Even so, "it is going to be hard for the FDA to ramp up and be more flexible internationally," he says. "This is an issue with the U.S. Patent Office, too, which has also been understaffed." The FDA has recently opened an office in India, where a number of companies, such as Ranbaxy and Dr. Reddy's, produce branded and generic medications for the U.S. and global markets.

Bright Future

Developments for the generic pharmaceutical industry are encouraging as more brand-name drugs come off patent and payers push for cost cuts in health care. In addition, an increase in FDA budget and staffing should begin to cut the backlog of branded and generic drug applications and increase the ability of the FDA to inspect facilities here and overseas as generic biologics get to market in the next few years. **B**

Freelance writer Amy E. Buttell of Erie, Pa., covers mutual funds for the magazine.