
America's generic pharmaceutical industry: Opportunities and challenges in 2006 and beyond

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Kathleen Jaeger

was named President and CEO of the Generic Pharmaceutical Association (GPhA) in April 2002. Prior to joining GPhA, she was a Partner in the Washington, DC firm of Kirkpatrick & Lockhart LLP.

Abstract The US generic industry, with annual sales of more than US\$22bn, is excited about the prospects and opportunities for the future. However, the industry must remain vigilant to efforts by some special interest groups that seek to delay the timely introduction of more affordable generic drugs today, and in the future. Among the issues that could affect the continued growth of the generic pharmaceutical industry are authorised generics; misuse of the Citizen Petition process; and imposition of measures in free trade agreements that could harm America's generic drug industry. While the generic industry is focused on ensuring a level competitive playing field by addressing these and other issues, it is also expending significant time and energy to open the door to the new, untapped opportunity for savings that would result from generic competition for expensive biopharmaceutical products.

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INTRODUCTION

America's generic pharmaceutical industry is entering a period of extended growth, and yet, the industry will face continued challenges as it works to provide more affordable medicines to American consumers, and increase its contribution in the expanding American healthcare environment.

In the nearly three decades since the passage of the Drug Price Competition and Patent Term Restoration Act (commonly referred to as the Hatch–Waxman Act), the US generic industry has grown into a

powerful force for affordable medicine. In 2005, the generic industry represented more than 56 per cent of prescriptions dispensed, yet only US\$0.13 of every dollar spent by Americans on prescription drugs. Today, the generic pharmaceutical industry records more than US\$22bn in annual sales, and of the top five US pharmaceutical companies, based on the number of prescriptions dispensed, the top four companies are generic pharmaceutical developers and manufacturers.

All economic signs are pointing to continued growth, which means more opportunities for consumers and healthcare providers to save billions of dollars each year through the increased availability of affordable generic medicines. This growth will be driven by a variety of factors.

First, in the United States there are enormous pressures to hold down healthcare

Kathleen Jaeger
Generic Pharmaceutical Association (GPhA), 2300 Clarendon
Boulevard, Suite 400, Arlington, VA 22201, USA
Tel: +1 703 647 2480
Fax: +1 703 647 2481
E-mail: KJaeger@gphaonline.org
Web: www.gphaonline.org

costs in general, and prescription drug spending in particular. All providers of healthcare, including federal and state-funded programmes, employers, insurers, and finally consumers, are feeling these cost pressures. Fortunately, generic drugs will continue to offer payers the opportunity to hold down monthly insurance premiums, out-of-pocket costs, and drug spending related to Medicare and Medicaid programmes.

Second, changes in the US Medicare prescription drug benefit, which went into effect on 1 January 2006, include modifications to prescription drug coverage under Medicare Part D. Millions of senior citizens have registered for the drug benefit programme, under which private companies provide the coverage and beneficiaries choose the drug plan and pay a monthly premium. Prior to the enactment of the drug benefit, many seniors did not have health coverage for their prescription drugs, forcing some to do without needed medicines due to high drug costs. The new drug benefit programme strongly encourages the use of affordable generics as a way to reduce costs for seniors.

Third, a record number of traditional pharmaceutical products will lose patent protection within the next five years, which will open the floodgates for significant competition from generic firms. In fact, blockbuster products valued at US\$22bn in 2006, US\$27bn in 2007, and US\$29bn in 2008 will lose patent protection. One analyst has suggested that the total sales of drugs coming off patent will exceed US\$160bn by 2015. This flood of patent expirations will create numerous opportunities for generic pharmaceutical manufacturers beyond the next several years. As a result of the large number of drugs expected to lose patent protection, analysts have predicted that the overall market for generic drugs could continue to grow at double-digit rates through the next five years.

The Generic Pharmaceutical Association (GPhA) represents the manufacturers and distributors of finished generic

pharmaceuticals, manufacturers and distributors of bulk active pharmaceutical chemicals, and suppliers of other goods and services to the generic drug industry. Through numerous programmes on the state, federal, and international level, GPhA has been aggressively advocating for affordable healthcare for consumers, addressing a multitude of obstacles that delay timely generic drug approvals, and contending with the brand pharmaceutical industry to keep a level playing field in the pharmaceutical market. The lowering of America's prescription drug bill by billions of dollars each year is achieved only by the robust competition effectuated by the generic industry.

In addition to these efforts, GPhA also recognises that education — of consumers, physicians, pharmacists, employers and insurers — is critical to ensuring public awareness that generics offer the same medicine and the same results, but at significantly lower costs. While some individual states have generic substitution rates in excess of 60 per cent, and a national average substitution rate of 56 per cent is admirable, there is still significant opportunity for growth in generic utilisation. Analysis has demonstrated that a 1 per cent increase in generic substitution would result in more than US\$4bn in additional annual savings in the US each year. As a result, GPhA also must concentrate on those activities that can result in increased utilisation of generic medicines across the nation.

CHALLENGES TO FUTURE GROWTH

The generic industry is excited about the prospects and opportunities for future growth. However, the industry remains concerned about acceleration of efforts by some special interest groups that would delay the timely introduction of more affordable generic drugs. Among the major concerns are the need to increase funding for the Food and Drug Administration (FDA) Office of Generic Drugs (OGD), which approves generic

applications; attempts by the brand industry to undermine generic patent challenges through the use of authorised generics; continued misuse of the Citizen Petition process to delay generic approvals; and the use of free trade agreements (FTAs) to impose measures that would harm America's generic industry, among other initiatives. GPhA is working to ensure that the need for affordable medicines trumps these special interests.

Increased funding for generic drug approvals

Today, more than 800 generic applications are languishing without approval due to lack of resources at OGD. Funding for OGD has remained relatively flat over the past several years, and the backlog of generic drug applications has continued to grow. OGD's workload has increased by 36 per cent, and the number of applications awaiting review is expected to increase with more than US\$100bn in brand products expected to lose patent protection by 2010. Additional funding would better enable OGD to process these applications more rapidly, and provide consumers with access to affordable generic drugs in a more timely fashion.

Cooperative efforts between the generic industry and OGD's staff have resulted in a streamlining of the approval process and better generic pharmaceutical applications. Yet, there is a practical limit to the number of initiatives that can be undertaken to streamline the process and increase productivity. Ironically, OGD takes, on average, more than 15 months to approve an 'abbreviated' generic application, while the agency approves priority new drug products in as little as five months and new therapeutic proteins in about seven months.

Increased appropriations would permit OGD to lift the current hiring freeze and invest in the staff and resources needed to expand its capabilities and reduce the backlog. Adequate funding for such a programme would facilitate timely approval of affordable medicines, increase generic utilisation and lead to greater savings to the healthcare system.

The return on investment from increased funding will pay significant and long-lasting dividends for all Americans — state and federal governments, employers, and individual consumers alike.

Authorised generics

When Congress created the US generic pharmaceutical industry in 1984, it recognised that a mechanism was necessary to ensure that brand products were not unfairly or unnecessarily protected from generic competition by inappropriate or unenforceable product patents. The complex system of brand drug patent approval is premised on what patent information brand companies submit to FDA for each brand pharmaceutical product. Recognising that this process is not adversarial, and that a check and balance was missing from brand drug patent approval, Congress created the patent challenge process that enabled generic companies to challenge drug patents through litigation that would result in the early introduction of generic medicines if the challenge was successful.

As part of this process, Congress determined that it was in the best interest of consumers to create the 180-day generic exclusivity incentive to encourage generic companies to challenge questionable or frivolous brand pharmaceutical patents. During the 180-day period, the generic company that successfully challenges the patent in court is exclusively permitted to compete with the brand company. Thereby, the 180-day exclusivity provision establishes a mechanism by which generic companies may recoup the significant costs of investment in product development and patent challenge litigation while also creating an incentive to undertake more patent challenges in the future. Because generic companies operate under significantly smaller margins than brand companies, the 180-day period is a critical time for a generic company.

The 180-day exclusivity provision has successfully accelerated consumer access to

affordable medicines. Over the past 20 years, generic manufacturers have undertaken numerous patent challenges as a result of the 180-day exclusivity incentive. Without this incentive to challenge patents, some brand companies would have evergreen patents resulting in lack of access to affordable generic medicines for consumers for many years to come. These successful patent challenges have generated tens of billions of dollars in savings for American consumers.

Authorised generics are a relatively new tactic used by the brand pharmaceutical industry to undermine this incentive and defy Congress' intent. Authorised generics — brand products masquerading as generics — are an increasingly common brand tactic aimed at discouraging generic companies from challenging questionable brand patents. Determined to maintain their market shares at all costs, brand companies recognised that by simply changing the labels of their products, they could compete directly against the generic during the 180-day exclusivity period. Because FDA considers authorised generics to be brand products, the authorised generic is not subject to the 180-day marketing exclusivity provision. Although the practice might sound relatively benign, these products take advantage of an unintended loophole in federal law that, if left unchecked, could result in fewer affordable medicines coming to market.

Brand companies argue that authorised generics merely foster competition and lower prices. Yet authorised generics tend to appear on the market only immediately at the start of the 180-day period and some are even removed from the market as soon as the 180-day period expires, when other true generics are allowed to compete.

The industry is committed to working with employers, payers, consumers and others to ensure that timely access to affordable generic medicines is not jeopardised. GPhA will continue to work with Congress to close loopholes in the Hatch-Waxman Act and

preserve this important incentive, before irreparable damage is done to the patent challenge process.

Citizen petition issues

Citizen petitions are a growing concern not only for the generic industry, but for FDA as well. Every US citizen has a constitutionally protected right to petition the federal government. However, some brand pharmaceutical companies, their lawyers, or other representatives routinely file citizen petitions against pending generic drug applications on the eve of product approval.

Upon receipt of a citizen petition, regardless of its merits, FDA typically delays approval of the generic drug application until the issue underlying the citizen petition can be reviewed and addressed. Citizen petition filings regarding generic drug applications have increased in recent years, sometimes substantially delaying generic drug approval times and consumers' access to affordable medicines. The vast majority of such petitions are without merit and do not result in any modification of the drug application approval requirements as they are ultimately denied, but not before they have their intended effect of extending brand companies' product monopolies.

The FDA itself has confirmed that there are examples of citizen petitions that appear designed not to raise timely concerns with respect to the legality or scientific soundness of approving a drug application, but rather to delay approval by compelling the FDA to take the time to consider arguments raised in the petition, whatever the merits, and regardless of whether the petitioner could have made the arguments earlier.

GPhA has been supportive of a bifurcated system in which generic drug application approvals would not be subject to delay due to pending issues raised in a citizen petition. In a letter sent to FDA in December 2005, GPhA pointed out that a bifurcated system would encourage early submission of legitimate citizen petitions and ensure timely

access to affordable medicines for consumers. Specifically, GPhA recommended several remedies to increase the efficiency and effectiveness of the citizen petition process, including stricter adherence to the requirement of responding to citizen petitions within 180 days; significant improvement of a formal 'tracking' method; and a requirement that the petitioner provide full disclosure of conflicts of interest, such as the petitioner's financial interests in the submission and/or approval of the petition.

Both FDA and Congress have recognised the inherent issues related to delaying generic competition through the abuse of the citizen petition process, and GPhA will continue to work with congressional and administrative leaders to ensure that this process does not delay generic competition.

Free trade agreements

The brand industry does not end its efforts to delay timely generic competition at US borders and has increasingly sought to manipulate FTAs as another means of obtaining its goals. Recent FTAs contain unlimited patent extensions, greater market exclusivity, and elimination of the requirement that a brand company disclose the best mode of practicing its invention: all dramatic divergences from US law.

For example, in Canada, the brand industry is promoting eight years of market exclusivity, which is three years longer than the market exclusivity provision in the North American Free Trade Agreement. In another example, Israel raised the ire of the brand industry by approving a measure that provided for five years of market protection for novel pharmaceutical drugs, even though this very standard is adopted in the United States. In Chile, the brand industry continues to try to impede implementation of a robust generic approval process by pressuring the government to adopt a complex patent linkage system that lacks generic access provisions.

In response, the generic pharmaceutical industry has become even more active on

international issues, heading off attempts by the brand industry to make changes in US patent and exclusivity laws under the guise of harmonisation with trade agreements. For example, the generic industry has called for clarification of provisions of the Central American Free Trade Agreement (CAFTA) that would have made it more difficult for Central American countries to obtain access to affordable medicines. The industry is also working to prevent the establishment of such provisions in the Colombia, Ecuador, Thailand, Malaysia, Korea, and other FTA negotiations.

Other threats to generic competition

Another potential threat to consumers' timely access to affordable medicines is patent reform. Congress has for some time been considering legislation that could make sweeping changes to the way patents are filed and how questionable patents are challenged. Some proposals could weaken the integrity of the US patent system by increasing the length of patent monopolies on expensive, branded drugs by eliminating several defenses to patent infringement currently available to generic competitors.

Reform proposals might also eliminate the 'best mode' requirement, under which the inventor must disclose in the patent application the most efficient known method for producing the invention. Elimination of this requirement would amount to *de facto* patent extensions, unduly prolonging the brand's monopoly.

GPhA has cautioned Congress on moving too quickly on patent reform and called for careful analysis to ensure that the legislation does not unintentionally harm the healthcare system.

GPhA also has focused on reducing some of the red tape that slows imports of active pharmaceutical ingredients (API) and other drug products from reaching their final destinations in a timely manner. The paperwork and documentation involved in

bringing API and various drug shipments into the United States has been particularly cumbersome and inconsistent in some US ports of entry. The focus of one proposal under consideration by the industry and FDA would provide assurance on the security of the shipment and prevent counterfeit materials from entering the United States. Companies would provide information on their supply chains to FDA and once FDA determined that the supply chain is authentic, secure, and unadulterated, the shipment would be considered prescreened, receive a lower risk status, and thus, be allowed to proceed without delay. The proposal would apply to both finished drug products and API.

The proposal also would establish time-frames for FDA to follow, such as a deadline for when the agency must respond to information it receives; limit the type of information required by FDA to that which is statutorily authorised; and encourage the use of tracking technologies to verify that shipments continued in the same stream of distribution.

GENERIC BIOPHARMACEUTICALS — AN UNTAPPED OPPORTUNITY FOR SAVINGS

While America's generic industry is focused on ensuring a level, competitive playing field, it is also expending significant time and energy to open the door to a new, untapped opportunity for savings through generic competition for expensive biopharmaceutical products.

Hatch–Waxman did not expressly anticipate the rapid development of biopharmaceutical products, which are generally protein molecules derived from living cells, such as antibiotics, insulin, and human growth hormone. Today, because a process for the approval of generic biopharmaceuticals does not exist, America is falling behind the rest of the world in this area.

Australia and the European Union (EU) have surpassed the United States in establishing guidelines for a generic

biopharmaceutical approval process. Two years ago, Australia approved a generic human growth hormone, which is now being marketed there, and the EU has already approved applications for generic biopharmaceuticals in 2006.

America's biopharmaceutical industry represents one of the most successful and fastest growing segments of US healthcare. Ten years ago, revenues for this industry were approximately US\$8bn. Today, biologics have annual revenues that exceed US\$30bn. By 2010, analysts estimate that biologic sales will exceed US\$60bn.

More than 150 biopharmaceutical drugs are currently marketed, including human insulin, interferons, human growth hormones and monoclonal antibodies. In the past year, more than 30 new drugs were approved, compared to just two in 1982. There are more than 370 biopharmaceutical drug products and vaccines currently in clinical trials targeting more than 200 diseases including cancer, Alzheimer's disease, heart disease, multiple sclerosis, AIDS, and arthritis.

Biopharmaceuticals are a major driver of skyrocketing prescription drug costs. Six products — Procrit[®], Epogen[®], Neupogen[®], Intron[®] A, Humulin[®], and Rituxan[®] — each generated sales of more than US\$1bn. And at least three new blockbusters are expected to join that list. The top three biopharmaceuticals — Neupogen, Epogen and Intron A — cost patients US\$23,098, US\$10,348, and US\$5,850, respectively, each year. As evidenced by these examples alone, generic competition for biopharmaceuticals has the potential to offer consumers substantial savings, while lowering America's healthcare bill.

A number of biopharmaceutical products developed during the 1980s have or will soon lose patent protection. Sources estimate that within the next five years, biopharmaceutical products with annual sales in excess of US\$10bn will lose patent protection and would be vulnerable to competition from generic biopharmaceuticals if an approval

process existed. Without such a process, prices will remain artificially high despite the loss of exclusivity.

A practical, timely, and cost-efficient regulatory approval process for generic versions of biopharmaceuticals is critical. Although generic manufacturers are free to invest in the development of their own biopharmaceutical versions of currently marketed brand name drugs, without a generic regulatory approval process, they will not be deemed substitutable for the brand version. In effect, the generic manufacturer will be adding a 'me-too' product into the marketplace, with no direct advantage to consumers, who would need to receive a specific prescription for the generic company's product.

The principles for an abbreviated approval pathway are clear. It must be based on sound scientific rationale that does not require unnecessary trials that have previously been conducted by the innovator. It must also serve the dual purpose of allowing for the demonstration of interchangeability with the brand product, while also allowing for the approval of a generic product without interchangeability.

Clinical study requirements must be directly related to the complexity of the molecule. For those biopharmaceuticals with minimal complexity, characterisation must be the cornerstone for approval. As products become more complex, characterisation combined with limited animal and clinical studies would be appropriate. For moderately complex biopharmaceuticals, clinical studies must be limited to the demonstration of comparability based on surrogate markers, and trials should only be as large as necessary to scientifically demonstrate comparability of the generic to the brand product. For highly complex biopharmaceuticals, characterisation, animal studies, and targeted clinical trials may be appropriate.

The abbreviated approval process for generic biopharmaceuticals must formally recognise this spectrum of complexity, and not require the same level of clinical data for

all. Approval of generic biopharmaceuticals cannot and should not be 'one-size-fits-all,' but be specific to the scientific complexity of the molecule in question. Assuring that the approval process appropriately ranks the complexity of biopharmaceutical products will be critical to prevent brand interests from 'gaming the system' at the expense of affordable competition that can generate billions in consumer savings.

The economic need is compelling. For example, in 2003, the average cost to a major US employer for a one-day supply of biopharmaceutical drugs was US\$45, while traditional drugs, including brand and generic, cost an average of US\$1.66 per day. Costs for specific treatments can run into hundreds of thousands of dollars annually. One of the most expensive biopharmaceuticals is Cerezyme, which is used to treat a genetic condition and is priced at an average of US\$170,000 per patient per year. In 2003, the cost per patient for one year's supply of Neupogen, a biopharmaceutical used in cancer treatments, was US\$23,098.

Affordable biopharmaceuticals, even if they represented only a modest segment of the US market, would create billions of dollars in savings each year. Despite this compelling argument, FDA continues to struggle with moving forward toward establishing an abbreviated approval process for generic versions of these medicines, and for years the agency has delayed the release of a White Paper and guidance documents.

The science to support generic versions of these products has been verified time and again during public workshops hosted by FDA. In June 2006, a significant first step was taken when FDA approved Sandoz's Omnitrope, a human growth hormone.

The Omnitrope decision clearly demonstrated that sound science exists to support the approval of generic biopharmaceuticals despite assertions from special interests to the contrary. The approval demonstrated that US generic companies have highly sophisticated research and development

capabilities and are ready to enter the US biopharmaceutical market, and that FDA already has the authority to approve such products.

It is GPhA's position that the 505(b)(2) Federal Food, Drug, and Cosmetic Act approval process, in conjunction with FDA's authority under the Public Health Service Act (PHS), already serves as a foundation for the approval of safe and effective generic biopharmaceuticals. Yet, the industry will continue to call on Congress to codify FDA's authority to approve generic biopharmaceuticals under section 351 of PHS.

Given the potential for tremendous healthcare savings, GPhA has been urging FDA to end the delay in releasing its guidances. It is imperative for the sustainability of the US healthcare system that the agency codify a regulatory pathway for the introduction of affordable biopharmaceuticals and issue its recommended scientific principles.

GPhA will continue to work with FDA and lawmakers to facilitate the codification of an abbreviated approval pathway to ensure that consumers will have access to these life-saving medicines. American consumers and healthcare providers cannot afford to wait.

OUR CHANGING INDUSTRY

The anticipated growth of the traditional generic pharmaceutical industry, and the potential introduction within the near-term of generic versions of biopharmaceutical products, represent unprecedented opportunities for America's generic industry. Yet, our industry continues to change and adapt to the increasingly competitive and cost-conscious marketplace.

One of the most visible changes is the consolidation of players within the generic industry. This merger and acquisition (M&A) activity is reshaping America's pharmaceutical environment, with several major combinations in the past several years.

Israel-based Teva Pharmaceuticals finalised its acquisition of IVAX Pharmaceuticals in January 2006. Sandoz, a division of Swiss drug

major Novartis, completed the acquisition of Hexal and Eon Labs in 2005. Watson Pharmaceuticals acquired Andrx Corp., and as this paper was being written Croatia-based Pliva was in play. Ranbaxy and Dr Reddy's, two India-based companies, also have been strengthening their presence through acquisitions in Europe.

Part of this M&A activity is driven by the need for adequate size and scale to more effectively compete on a global basis. Some are driven by the need to maximise cost structure in an increasingly competitive marketplace. Some acquisitions also have been driven by the need to acquire complementary products, technologies and drug delivery systems. And some are focused on securing a global presence given the emerging markets of eastern Europe, Russia, and China, among others, in light of increased demand in industrialised nations and the need for global healthcare cost-cutting.

Analysts predict that this activity, on both a large and small scale, and a regional and international basis, will continue into the foreseeable future as the competition for generic drugs becomes even more intense.

A BRIGHT FUTURE, WITH CHALLENGES

Clearly, America's generic industry is in a golden age. Opportunities to increase substitution based on cost-consciousness will expand. The large number of drugs coming off patent within the next several years will result in intense competition and substantial savings for consumers. And yet untapped opportunities for competition in biopharmaceuticals are likely to dramatically reshape the US prescription drug landscape. While GPhA and the US generic drug industry must continue to thwart efforts by brand companies to delay competition, and continue to work to educate consumers about the value of generic medicines to increase substitution rates, the future, for the next several years, is one filled with opportunities for the generic industry and its allied companies.