



Regulation of Follow-on Biologics

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Biopharmaceutical products, with U.S. sales in 2006 amounting to about \$40.3 billion, are increasingly central to the treatment of major health problems affecting Americans.¹ Since modern bio-

pharmaceuticals date back to the 1980s, the first generation of such drugs has begun to lose patent protection (see table). In other parts of the world, governments have crafted regulations defining the terms of competition from “imitator,” or generic, products. Many analysts have expressed concern that without new U.S. regulations, patent expirations may not be accompanied by the introduction of competing, lower-cost biologic agents — or that imitator products might be approved without sufficient proof of efficacy and safety, posing threats to public health. Although

some biopharmaceutical products are nearly as simple as traditional small-molecule drugs, the vastly increased complexity of others means that it will be more difficult to ensure that an imitator product is biologically and functionally equivalent to the original. Because it may not be possible to create “true” generic versions of biopharmaceuticals, the term “follow-on biologic” is often used to refer to a new version of an existing biopharmaceutical that uses the same mechanism of action and treats the same clinical indications as the original.

The Drug Price Competition

and Patent Term Restoration Act of 1984 (the Hatch–Waxman Act) offers a starting point for considering regulation of the use of follow-on biopharmaceuticals (see box). This law, which is widely considered a success, governs the use of traditional generic medications. It establishes a low-cost path to market for generic imitators and requires their manufacturers to demonstrate bioequivalence but not to repeat human trials demonstrating efficacy and safety. The law also establishes minimum periods of market exclusivity for brand-name products.

It took a number of years for the Hatch–Waxman Act to exert its full effect on prescription-drug prices. At first, many physicians were reluctant to view generic drugs as fully interchangeable with brand-name products. Dur-

Top-Selling Biopharmaceuticals Approved before 1993.*			
Drug	Indication	Approval Date	2003 Sales \$ (millions)
Humulin (human insulin)	Diabetes	October 1982	1,060
Intron A (interferon alfa-2b)	Cancer, infection	June 1986	1,851
Humatrope (somatropin)	Growth failure	March 1987	371
Infanrix (diphtheria–tetanus–pertussis vaccine)	Immunization against diphtheria, pertussis, and tetanus	March 1987	551
Epogen (epoetin alfa)	Anemia	June 1989	2,435
Engerix-B (hepatitis B vaccine)	Immunization against hepatitis B	August 1989	684
Botox (botulinum toxin type A)	Cervical dystonia	December 1989	564
Epogin (epoetin beta)	Anemia	April 1990	551
Procrit (epoetin alfa)	Anemia	December 1990	3,984
Neupogen (filgrastim)	Neutropenia	January 1991	1,267
Cerezyme (imiglucerase)	Gaucher's disease	April 1991	739
NovoSeven (recombinant factor VII)	Hemophilia	April 1992	589

* The patents on these products expire after 20 years; most patents are applied for during the drug-development stage. Data are from *MedAdNews*, "Top 200 World's Best Selling Medicines" (2004;23 (5):60-4).

ing the late 1980s, a brand-name drug generally lost about 15 to 30% of its sales volume in the first 2 years after its patent expired.² In contrast, when Eli Lilly lost patent protection for the antidepressant drug Prozac (fluoxetine) in 2001, generic competitors garnered more than 70% of Prozac's market within 2 months.³ Today, brand-name drugs that face generic competition rapidly lose market share, and prices of generic products generally fall to

25 to 50% of the original brand-name prices.⁴ Although intense price competition reduces the financial returns for brand-name drugs, the patent period provides important protections, and the investment of U.S. drug companies in research and development has grown rapidly — from \$26 billion in 2000 to about \$43 billion in 2006.⁵

It was possible to achieve the benefits of the Hatch–Waxman Act because the Food and Drug

Administration (FDA) could review data establishing bioequivalence and be confident that data on the safety and efficacy of the original drug would apply to generic versions as well. Biopharmaceuticals are frequently much more complex than small-molecule drugs, and their manufacture often entails the use of live cells and complicated biologic processes that are difficult to replicate. Indeed, the manufacturing process can be a trade secret. Thus, obtaining evidence that a drug is similar to and will have the same effects as the original is more complicated for biopharmaceuticals.

The European Union is ahead of the United States in dealing with these issues, although the FDA has begun to address them in an ad hoc fashion. Any U.S. policy in this arena will no doubt share some basic features with

Key Provisions of the Hatch–Waxman Act.

- Creates an abbreviated approval process for generic pharmaceuticals
- Requires the manufacturers of generic drugs to demonstrate bioequivalence to brand-name products but allows them to rely on originators' clinical trials to establish safety and efficacy
- Allows testing before the originators' patents expire
- Creates an incentive for generic-drug manufacturers to challenge originators' patents
- Sets forth a process for handling patent disputes
- Defines the conditions for patent extensions

the one established in Europe. This means that a multistage process will probably be developed and that the FDA will be given a great deal of discretion in deciding how much data and testing are enough to establish attainment of the key standards of safety and efficacy — similarity and interchangeability — for follow-on biologics. Having such discretionary powers will also permit the FDA to incorporate rapidly changing technology into measurement and testing procedures.

The differences between follow-on biologics and generic pharmaceuticals suggest that market competition may also be very different. Bringing a product to market will be less certain and more costly for follow-on biologics than it is for generic drugs. The fixed costs of establishing a manufacturing plant are higher, and the variable manufacturing costs will be higher as well. In addition, biopharmaceutical production facilities must be scrutinized more closely than generic-drug manufacturing facilities. The uncertainty and costs of developing manufacturing capability and addressing the requirements of the regulatory process may reduce the number of firms seeking to produce follow-on biologics. An open question is whether there will be enough sellers to generate active price competition: economic research has generally shown that most of the benefits of price competition are not obtained until four or five firms enter a market. The expected profitability of developing a follow-on biologic will be paramount. The speed of entry will also depend

on how much information about their manufacturing processes the makers of original biopharmaceuticals will be required to report. Analysts predict that more complicated molecules will have less competition from follow-on products, which will enter the market more slowly than traditional generic pharmaceuticals.

Finally, the returns to research and development for biopharmaceuticals are unclear. Suppose, as has been suggested, that regulations governing the approval of follow-on biologics guarantee 12 years of exclusivity for brand-name biopharmaceuticals and that the technological and economic environment dampens potential competition. These factors would create a favorable climate for investment in research and development, weakening the case for special provisions. On the other hand, it appears that the costs and risks associated with developing biopharmaceuticals exceed those for small-molecule drugs. So the net effect on expected returns on investment remains an open question. The years of exclusivity granted to brand-name products will probably be an important driver of these returns and pose a barrier to competition from follow-ons. It is premature to assume that 12 years of exclusivity will be needed to preserve innovation in the biopharmaceutical arena — and putting off price competition is risky because of pressures on public budgets and the expanded role of the Medicare program in purchasing biopharmaceuticals.

The prospect of the loss of patent protection for tens of bil-

ions of dollars' worth of biopharmaceuticals increases the urgency of the need for a regulatory policy that promotes price competition and preserves the safety and efficacy standards that Americans expect from prescription drugs. In my opinion, the Hatch-Waxman framework is not sufficient to cover both relatively simple biopharmaceuticals and very large and complex molecules — a new regulatory framework is needed. Because of the need for complex, situation-specific judgments, the FDA should be granted a great deal of discretion. The conflicting goals of bolstering price competition in biopharmaceutical markets and preserving the incentives for innovation call for a nuanced policy that must be based on the best current science and key features of the economics of biopharmaceutical markets — not on the impassioned claims of the interested parties.

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