

STILL AWAITING THE ‘BIOSIMILARS’ REVOLUTION

Despite recent efforts, the United States remains a long way from a Hatch–Waxman breakthrough for biologic drugs.

◆ BY HENRY I. MILLER

Generic medicines are a critical element of Americans’ health care. Since 1984, the marketing of generic versions of chemically synthesized “small-molecule” drugs such as those used commonly to control diabetes, blood pressure, cholesterol, and pain, has been governed by legislation commonly known as the Hatch–Waxman Act. By allowing approval of generics through an abbreviated and less costly pathway than for “brand-name” innovator drugs—a route that does not require new clinical trials but only a demonstration of “bioequivalence”—this legislation has balanced the need to preserve the pharmaceutical industry’s incentive to innovate with the benefits of competition.

The result has been a robust and hugely important generic drug industry. More than four of every five drug prescriptions are for generic drugs, which saves consumers over \$200 billion annually. The price effect of newly available generic drugs is often rapid and impressive: when the first generic copy of a typical small-molecule drug reaches pharmacies, there is typically about a 30 percent drop in price, often reaching 80 percent as additional generic versions appear. Thus, brand-name drugs like Lipitor and Prilosec that were economic blockbusters while their patents were intact have seen their market share and revenues plummet once generics became available.

When the pathway for generic drugs was established 30 years ago, the class of drugs called “biologics”—complex molecules derived from living cells, and including vaccines, antibodies,

toxins, antitoxins, and allergenic products—was inconsequential compared to simpler small-molecule drugs. Today, biologics are common. Each year since 2010, they have represented the majority of new drugs that come onto the market. They account for more than 20 percent of U.S. drug expenditures, with worldwide sales over \$150 billion annually.

In 2009, Congress passed the Biologics Price Competition and Innovation Act (BPCIA), which was supposed to begin the process of creating a generic drug–like pathway for follow-on biologics, or “biosimilars.” The objective was, of course, to replicate the success of Hatch–Waxman and stimulate the same sort of competition that lowers the price of small-molecule drugs after patents expire.

Passage of the BPCIA was accompanied by glowing predictions of cost savings. The Congressional Budget Office estimated that biosimilars would reduce total drug expenditures by \$25 billion over 10 years. Steve Miller of Express Scripts, the nation’s largest pharmacy benefit management firm, was far more bullish, predicting that cost savings could be \$250 billion by 2024.

The reality is likely to be far less rosy, thanks to the chemical nature of biologics. Because the most profitable of them are made in living cells—which are usually bacteria, yeast, or cultured mammalian cells that have been reprogrammed to synthesize the drug by means of the insertion of new genetic material—the choice of cells and purification methods determines the nature and amount of contaminants in the final formulation. Nothing is ever 100 percent pure, but it is much easier to come closer to that goal with small molecules. For generic versions of small molecules, the manufacturer must only demonstrate “bioequivalence,” the absence of significant differences from the original drug in its availability at the site of its action (for example, in the blood

HENRY I. MILLER, a physician and molecular biologist, is the Robert Wesson Fellow in Scientific Philosophy and Public Policy at Stanford University’s Hoover Institution. He was an FDA reviewer and the founding director of the agency’s Office of Biotechnology.



or gastrointestinal tract). Moreover, for biologics, phenomena such as protein folding, enzymatic modifications, and impurities inevitably introduce variation—sometimes with unexpected results. Experience has shown that even minuscule differences in the substances that accompany—or contaminate—the active drug substance can be clinically significant.

SMALL DIFFERENCES HAVE LARGE EFFECTS

The U.S. Food and Drug Administration announced in 2012 “an abbreviated pathway that will depend on existing data” for biosimilars—if “*there are no clinically meaningful differences*” from the original product. That requirement ensures that in spite of many predictions to the contrary, for the foreseeable future the availability of this new biosimilar pathway will neither significantly change the drug development landscape nor put a significant dent in escalating medical costs.

A significant but often overlooked fact is that the FDA’s involvement with biosimilars is not new. Over many years, regulators have already approved a small number of follow-on biologics. This experience offers valuable insight into how regulators view biosimilars. Scientific considerations dictated that all of the biosimilars required a substantial amount of laboratory and clinical testing—a far more

elaborate and expensive process than is required for small-molecule generics. There is no reason to think that the FDA’s approach to such products has changed; quite the contrary.

The FDA’s experience with biologics, both new and follow-on varieties, is revealing. When I was a medical reviewer at the FDA in the 1980s, a completely unexpected side effect occurred during the clinical testing of a new formulation of human growth hormone synthesized in bacteria. (At the time, commercial growth hormone was purified from human pituitary glands obtained from cadavers.) During the first clinical study on healthy volunteers (who, ironically, were senior executives of the drug company), the drug caused extreme pain at the injection site, fever, and abnormalities in blood chemistry diagnostic of inflammation. The problem resulted not from any anomaly in the growth hormone molecule itself, but from a low-level contaminant that, when injected into human subjects, stimulated white blood cells to release a substance that caused the signs and symptoms. Because of the indirect mechanism of its toxicity and its specificity for human cells, the contaminant had been undetectable in the standard, sophisticated screening tests used to assess a drug’s safety and in studies in animals. The problem only appeared when the drug was injected into humans.

Another vivid example of the potential problems with biologics

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occurred between 2001 and 2003 when two versions of a biologic called epoetin alfa, which treats anemia, were sufficiently different that one of them caused a 30-fold greater frequency of a severe kind of anemia. The drugs were supposed to be the same, but the clinical outcomes were very different.

Cognizant of such phenomena, the FDA has long considered that even minor changes in the production of biological drugs—including the same isolation and purification procedures applied at significantly larger scale than previously—yield a distinct, new drug that must undergo an independent demonstration of safety and efficacy. For example, several years ago the FDA reviewed an application to manufacture a biological used to treat Pompe disease—a debilitating inherited disorder—in a new, larger-scale manufacturing facility. Although the drug was produced by the same company with exactly the same process as at the smaller scale, the FDA considered the larger-scale version to be a new product and even required that it adopt a different name; the two products are marketed as Myozyme and Lumizyme.

The head of the FDA's drug center, Janet Woodcock, has acknowledged in congressional testimony the scientific and technical challenges posed by biosimilars. She said that regulators “will be influenced by the extent to which the follow-on product can be demonstrated to be sufficiently similar (structurally, functionally, and clinically) to an approved protein product to permit some degree of reliance on the findings of safety and effectiveness for the approved product.”

Woodcock also emphasized the importance of possible immunogenicity—the stimulation of an immune response (which can inactivate the drug and cause serious side effects)—by a biosimilar drug. She noted that “the ability to predict immunogenicity of a protein product, particularly the more complex proteins, is extremely limited,” and concluded that “therefore, some degree of clinical assessment of a new product's immunogenic potential will ordinarily be needed.”

BIOSIMILARS REQUIRE CLINICAL TRIALS

Three key government documents reinforce Woodcock's observations. First, the BPCIA itself defined biosimilarity to mean “the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and that “there are *no clinically meaningful differences* between the [biosimilar] biological product and the reference product in terms of the safety, purity, and potency of the product” [emphasis added].

Second, in the *Federal Register* in October 2010, the FDA acknowledged that although the BPCIA expresses the hope for “appropriate reliance on what is already known about [an earlier version of] a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing ... the implementation of an abbreviated approval pathway for biological products can present challenges given the scientific and technical complexities that may be associated with the larger and often more complex structure of biological products.”

The third publication, a 2011 article in the *New England Journal of Medicine* by four senior FDA officials, elaborated on the earlier statements:

- “Generally, therapeutic proteins must have a specific set of structural features (e.g., amino acid sequence glycosylation, protein folding) essential to their intended effect, and slight modifications can affect their performance in humans.”
- “Inadvertent chemical modifications can affect their immunogenicity.”
- “Additional animal and clinical studies will generally be needed for protein biosimilars for the foreseeable future.”
- Before regulators can even advise on required animal and human studies, “the FDA should already have completed an in-depth review of comparative analytic characterization and in vitro data.”
- “The FDA process for biosimilars must include product-specific safety monitoring” because “pharmaceutical companies will make manufacturing-related changes to biologics periodically throughout their lifecycles, and even small changes could affect safety or efficacy.”

The bottom line is that clinical trials—which may need to be large in order to achieve sufficient statistical power—will generally be required to demonstrate the efficacy and especially the safety of biosimilars before the FDA approves them. Interestingly, last July Sandoz, the generics subdivision of Novartis, filed the first application for approval of a biosimilar via the new pathway. Called Zarzio, it is a follow-on version of Amgen's Neupogen, a protein that stimulates the bone marrow to produce infection-fighting white blood cells when their numbers have been reduced by cancer chemotherapy. It will be informative to see how the FDA treats this product, which boasts significant post-marketing, real-world clinical data outside the United States. It has been marketed in more than 40 countries, which has generated nearly 6 million patient-exposure days of experience, and has been used in Europe since 2008. In addition, last December Sandoz reported that in a Phase 3 double-blind clinical trial on 218 patients, Zarzio and Neupogen were indistinguishable. In January the FDA's Oncologic Drugs Advisory Committee unanimously recommended approval. All of this argues that there are “no clinically meaningful differences” between Zarzio and Neupogen. I expect it to be approved in the first half of this calendar year.

A second application for approval via the biosimilars pathway was filed last August by South Korea's Celltrion for its biosimilar of Johnson & Johnson and Merck's anti-inflammatory blockbuster Remicade. Celltrion said that after prior consultation with the FDA, it conducted additional clinical trials—which started in October 2013 and lasted six months—to show that its product meets the criteria for approval.

In the future, new analytical methods will facilitate the development, manufacture, and regulatory approval of biosimilars. For example, a research article by FDA scientists published last

year showed that “small segments of DNA-like molecules called aptamers can be used in an efficient and practical method to compare the conformations of a therapeutic protein during drug development and quality control testing.” As discussed above, an important concern about biosimilars is the possibility that small differences from the reference product could cause immune responses to altered three-dimensional sites on the surface of the follow-on version of the drug, and the new technique may be useful to detect such subtle alterations. It appears to be superior to standard antibody-based, quality-control tests currently used for that purpose. But such scientific advances will need to undergo extensive validation studies before they can be considered a reliable predictor of effects in vivo and eliminate the need for clinical data.

For now, the high costs involved in planning, conducting, and analyzing the results of clinical trials will prevent a stampede to seek approvals via the new pathway; in fact, several major drug companies are pursuing the development of biosimilars as though they were completely new, independent, and distinct products. Consequently, those drugmakers have expressed their intention to submit a new Biologics License Application to obtain marketing approval, rather than an abbreviated submission via the biosimilars pathway.

The bottom line is that for the time being, from a regulatory perspective, most follow-on versions of an approved biological product will be regarded as, in effect, a completely new drug. Development costs will be higher and there will be far fewer biosimilars developed than generic versions of small-molecule drugs. Even under the best of circumstances, for the foreseeable future, savings to federal entitlement programs, insurers, and patients will surely be much more modest than some of the hyperbolic predictions made by politicians and others.

BIOSIMILAR ADOPTION PATTERNS

An interesting take on follow-on biologics or biosimilars that obtain marketing approval was presented by *Forbes* staff writer Matthew Herper in an article last June. He cited the prediction by global consultancy ZS Associates that the gain in market share of newly approved biosimilars “will depend on the disease being treated and whether decisions are being made by physicians and patients or by hospital administrators.”

Herper described several examples of the introduction of biosimilars that have had very different outcomes with respect to market share. The first was the 2007 challenge to Pfizer’s human growth hormone drug Genotropin by Omnitrope, produced by Sandoz:

Initially, there was little use of Omnitrope, even though Sandoz had priced it at 40% less than branded Genotropin. In the U.S., traditional generics get automatically substituted by the pharmacists unless a physician suggests otherwise. With growth hormone, physicians and patients initially had no reason to switch. What helped Omnitrope gain market share was a

series of efforts one would expect in a war between two brands. Patient assistance programs helped people afford the medicine, rebates to health plans made it cheaper to insurers, and new clinical trials made doctors more comfortable prescribing it. Even with that 40% discount, Omnitrope still has less market share than Genotropin.

In a second example, doctors and patients were again resistant to switching to the biosimilar:

That was the case when Shire launched Vpriv in the midst of a shortage of Genzyme’s Cerezyme, for Gaucher’s disease, a rare disorder of the bones and connective tissue. Doctors and patients switched initially because of the supply problems, but then they switched back—even though Vpriv was 15% cheaper. They were loyal to the original product, and no one forced them to switch on the basis of price, which was handled by insurers and patient assistance charities funded by drug makers.

As Herper observed about such cases, “copycat drugs may have trouble making a dent, lowering drug costs for the system as a whole, or hurting established players.”

The third example was the introduction of Novartis and Momenta Pharmaceuticals’ biosimilar version of Sanofi’s anti-coagulant Lovenox:

The biosimilar, enoxaparin, rapidly took most of the branded drug’s market share thanks to its 14% discount to the original brand. That’s because patients don’t choose which blood thinner they get in the hospital. The decision of which to buy was largely made by hospital administrators who saw no difference between the products except for price.

Thus, the conundrum of biosimilars is far more complex than Congress’s mandating and the FDA’s announcing a regulatory pathway for biosimilars. Scientific considerations and previous experience argue for certain constraints.

CONCLUSION

Eventually, the availability of biosimilars will spur competition and reduce prices somewhat. Because of advances in technology, some of the follow-on products will likely be superior to the original brand-name biologics. But for now, the new regulatory pathway for most biosimilars will neither be significantly abbreviated nor have a large effect on burgeoning health care costs. R

READINGS

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- “Developing the Nation’s Biosimilars Program,” by Steven Kozlowski,

Janet Woodcock, Karen Midthun, and Rachel Behrman Sherman. *New England Journal of Medicine*, Vol. 365, No. 5 (August 4, 2011).

■ “What Will Happen When Biotech Drugs Go Generic?” by Matthew Herper. *Forbes*, June 13, 2014.