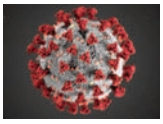

PERSPECTIVE

The Feds Act to Boost Competition in the Biosimilars Market

by Henry I. Miller, MD

Significant adoption of this class of drugs could save billions in healthcare costs.

Innovating new drug development is an expensive and uncertain business, typically taking 10-12 years and costing, on average, $2.55 billion to bring a new product to market. The risks are enormous, and deserve significant financial rewards; at the same time, it's undeniable that the costs of many new, complex drugs are high and possibly unsustainable. In the near future, one critical, emerging pricing issue will be how rapid is the uptake of a blockbuster class of drugs called "biosimilars," which can be thought of as generic versions of biologics, drugs that are complex biological molecules derived from living cells. Typical biologics include vaccines, gene therapy, blood and blood components, antitoxins, and allergenic products.

Importance of Generic or "Follow On," Versions of Brand-Name Drugs

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 innovator, or brand-name, drugs—a route that does not require new clinical trials but only a demonstration of "bioequivalence"—this legislation has balanced the need to preserve 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 filled are for generic drugs, which saves consumers over $200 billion annually. The impact 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% drop in price, often reaching 80% as additional generic versions appear. Thus, brand-name drugs like Lipitor and Prilosec that were economic blockbusters while their patents were intact and they had the market to themselves have seen their market-share and revenues plummet once generics became available.

Biosimilars

When the pathway for generic drugs was established 30 years ago, the class of drugs called "biologics" was inconsequential compared to simpler small molecule drugs, but now they are common. Each year since 2010, they have represented the majority of new drugs that come onto the market, and they account for more than 20% of U.S. drug expenditures, with global sales topping $150 billion annually. In 2018, eight of the top 10 drugs by worldwide sales were biologics. Hoping to replicate for biologics the success of Hatch-Waxman, 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 to 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

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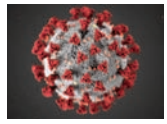


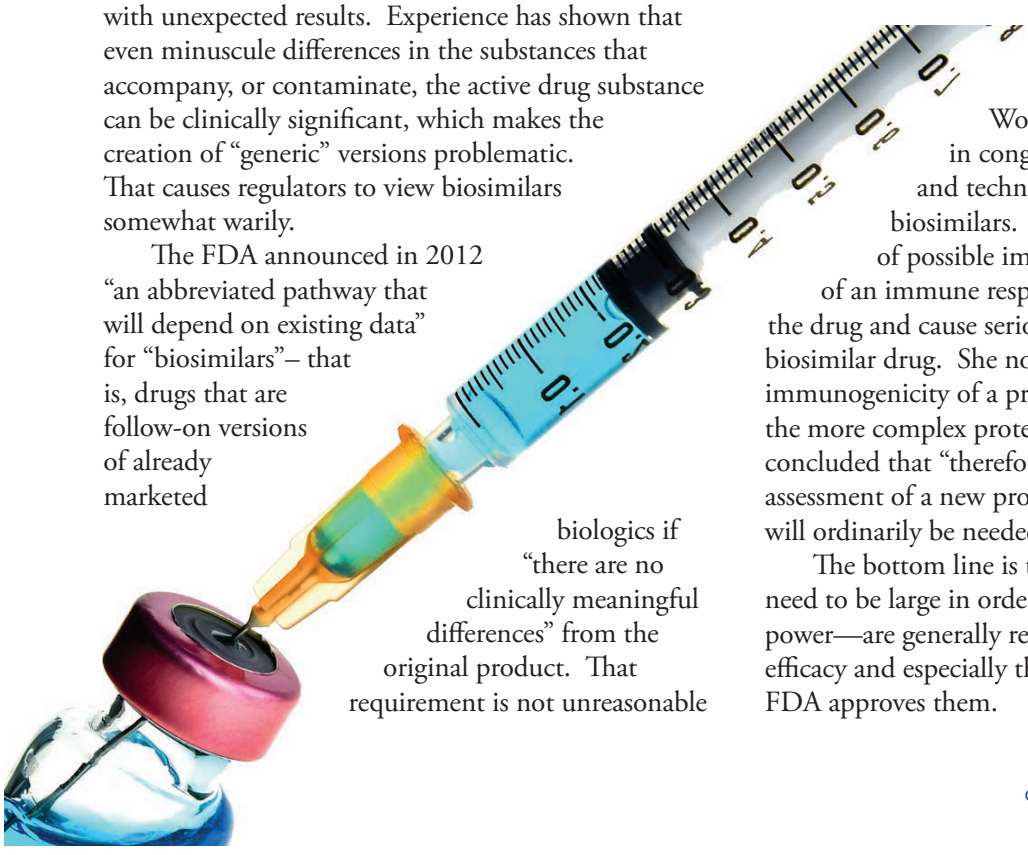
drug expenditures by $25 billion over 10 years; Steve Miller, MD, of Express Scripts, was far more bullish, estimating that cost savings could be a whopping $250 billion by 2024.

Looking primarily through a regulatory lens, I predicted five years ago that these predictions were far too optimistic. Indeed, the reality is likely to be far less rosy, thanks to several factors in addition to regulation – chemistry, patents, and a misinformation PR blitz by the competition.

Regulators Are Wary of Biosimilars

Scientific considerations make biosimilar replicas somewhat complicated. Biologics are generally made in living cells, which are usually bacteria, yeast or cultured mammalian cells that have been reprogrammed, or genetically engineered, 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% pure, but it's much easier to get 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, or innovator, drug in its availability at the site of its action (for example, in the blood or GI tract). However, for biologics, protein folding, various kinds of 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, which makes the creation of "generic" versions problematic. That causes regulators to view biosimilars somewhat warily.

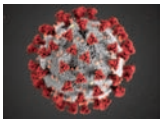
The FDA announced in 2012 "an abbreviated pathway that will depend on existing data" for "biosimilars"– that is, drugs that are follow-on versions of already marketed biologics if "there are no clinically meaningful differences" from the original product. That requirement is not unreasonable but it ensured that in spite of many predictions to the contrary, the availability of this new biosimilar pathway has neither significantly changed the drug development landscape nor put a significant dent in escalating medical costs.



An explanation of that requires some background. The FDA's involvement with biosimilars is not new; even before the 2012 policy was announced, over many years, regulators had already approved a small number of "follow-on biologics"—biosimilars by another name. This experience offers important insights into how regulators view biosimilars: Scientific considerations dictated that all of them required a substantial amount of laboratory and clinical testing—a far more elaborate, expensive process than has been required for small-molecule generics. There is no reason to think that the FDA's approach to such products has changed; quite the contrary, in fact, and this is reflected in the approval numbers. The first U.S. biosimilar was approved by the FDA in 2015, and as of January 15, only 26 had been approved. (This compared with 71 by the European Medicines Agency.)

Why the discrepancy? The FDA has long considered that even minor changes in the production of biological drugs—including even 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. The head of FDA's drug center, Janet Woodcock, MD, has acknowledged in congressional testimony the scientific and technical challenges posed by biosimilars. She emphasized the importance of possible immunogenicity—the stimulation of an immune response (which can both 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."

The bottom line is that clinical trials—which may need to be large in order to achieve sufficient statistical power—are generally required to demonstrate the efficacy and especially the safety of biosimilars before FDA approves them.



Economic Obstacles to Biosimilars Usage

There are also various non-scientific, non-regulatory economic factors that create disincentives to the uptake of biosimilars once they are approved. Economist Wayne Winegarden explains two of them:

One of the more important obstructions is the current "buy-and-bill" reimbursement system that dis-incents lower-cost biosimilars. Under this system, providers purchase medicines and then, once the medicines have been administered to the patients, bill insurers for the costs of the medicine plus their mark-up. The provider mark-up is typically a percentage of the medicine's price. Since a biosimilar's price is less than a biologic's price, providers lose money when they prescribe a lower-priced biosimilar medicine instead of a higher-priced biologic medicine. These losses are not *de minimis* either. A 2017 study found that in the case of one medicine class, infliximab, broad adoption of the biosimilars could decrease providers' profits by as much as $100 million.

Next, insurance plans commonly include fail-first policies. Typically, the purpose of fail-first policies is to require patients to use lower-priced generic medicines first, then, only if the generic medicines fail to sufficiently help the patients, can a more expensive branded medicine be prescribed. As applied to biosimilars, however, fail-first policies work in reverse. In this case, the insurance clauses will only allow patients to use the less expensive biosimilars if they first failed on the more expensive biologics. Thus, as currently applied, fail-first policies bias the market against less expensive biosimilars, harming competition in the process.

Another factor inhibiting the uptake of biosimilars is patents, which protect market share and the pricing power of the brand-name biologics, most of which haven't been on the market long enough for their patents to expire, at which time competitors would be permitted to launch cheaper biosimilars. (For many brand-name biologics, the protection afforded by patents will soon expire, however.)

Finally, the uptake of biosimilars has been slowed by several strategies devised by the manufacturers of the brand-name biologics in order to retain market share. For example, they have inhibited the sales of biosimilars by gaming the rebate system: In order for a healthcare insurer to receive rebates that lower its cost per prescription for brand-name biologics, it is forced to agree to contracts that exclude biosimilars or, at least, provide the brand-name biologic with preferential placement on its drug formulary, which dictates how much patients pay at pharmacies.

Why would insurance companies enter into such arrangements? Possibly because biosimilars are viewed skeptically, as a result of a kind of whispering campaign about them, as described below.

Although the BPCIA states explicitly that a biosimilar must be highly similar to, have the same mechanism of action as, and have no clinically meaningful differences from the reference product, that has not deterred some makers of the more expensive brand-name products from raising theoretical concerns about the safety and efficacy of biosimilars. They claim that their goal is solely to inform and protect patients, but as H.L. Mencken said, "When someone says 'it's not about money', it's about money."

The Feds To the Rescue?

The FDA and Federal Trade Commission intend to ensure that the information about biosimilars is not inaccurate or misleading. In a joint statement on February 3, 2020, they announced a partnership aimed at supporting the adoption of biosimilars and interchangeable products by deterring what they called "anti-competitive business practices," such as communications that make a "false or misleading comparison between a reference product and a biosimilar in a manner that misrepresents the safety or efficacy of biosimilars, deceives consumers, or deters competition."

Also according to the statement, the FTC will use its authority to obtain and review patent settlement agreements between the manufacturers of reference (original) products and biosimilars, and will determine whether they include, among other things, anti-competitive reverse payments that curb or prevent the introduction of lower-priced drugs into the marketplace.

Conclusion

The bottom line is that biosimilars have great promise to moderate drug costs but face obstacles. Economist Wayne Winegarden estimates that small-molecule generic drugs "saved the U.S. health system $1.67 trillion between 2007 and 2016 alone," and his analysis indicates that with increasing market share of currently approved biosimilars, the savings could run well into the billions. At least in the short-term, the obstacles are imposing, however, and only time will tell whether biosimilars will realize their potential. **MM**