Core Concepts: Biosimilars

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In September, a drug called Zarxio became available in the United States. More than just the debut of another drug, Zarxio's arrival introduced the US market to a new family of pharmaceuticals called "biosimilars," or "follow-on biologics." Biosimilars, which are already on the market in Europe and Asia, have the potential to reduce the cost of treatments for serious illnesses and could have an impact on patients, insurers, and pharmaceutical companies.

Biosimilars are biologic drugs—as opposed to chemical drugs, as in the case of generics—that deliver the same clinical benefits as a biologic drug already on the market. Zarxio, manufactured by Novartis-owned Sandoz, has the same effects on patients and the same safety profile as Amgen's biologic drug Neupogen, first approved in 1991, which lowers infection risk in patients undergoing chemotherapy by boosting the white blood cell count. At its launch in early September, Zarxio's cost was about 15% lower than that of Neupogen. In Europe, where the first biosimilars became available in 2006, the discount due to the drugs is typically 25% or less (1).

A report published in 2014 by the nonprofit Rand Corporation predicts that over the next decade, biosimilars will decrease overall direct spending on biologics in the United States by $44 billion (2). And Express Scripts, a pharmacy benefit manager, predicted in the same year that the approval of 11 specific biosimilars—including Zarxio—would lead to a savings of $250 billion over the same time period.

How those savings will decrease patients' costs, however, will take a few years to suss out, says Andrew Mulcahy, an associate policy researcher at Rand Corporation and lead author on the report (2). After a biosimilar enters the market, the price of the reference product will probably go down, according to Mulcahy. "That's a good thing for plans and payers," he adds, "and a good thing for patients, too. For a lot of these biologic drugs, patients are out-of-pocket thousands of dollars."

At the same time, Mulcahy cautions that biosimilars are "new to the FDA [Food and Drug Administration], new to manufacturers, to court, to payers, to patients, and to prescribers." That means he still sees a lot of uncertainty in the market.

The development of biosimilars should have a big impact on patients, insurers, and pharmaceutical companies for years to come. Image courtesy of Shutterstock/Sasa Komlen.

Biosimilar vs. Generic

Under current law, a biologic drug is protected against competition for 12 years after approval by the FDA. After that, other manufacturers can request approval for biosimilars that deliver the same benefits. Like generics, biosimilars compete against brand-name drugs that no longer have exclusive rights. But the two families of drugs differ under the hood.

Generics are copycats of chemical drugs that contain the same small-molecule active ingredients. Small-molecule drugs include, for example, statins, antihistamines, and oral chemotherapies. Generic versions have the same dosing guidelines and strength, and pharmacies can substitute generics for the trade-name drug without an additional prescription.

Biosimilars, on the other hand, imitate biologic drugs, which have large and complex protein molecules. They include vaccines, monoclonal antibodies, insulin, and a slew of other cancer therapies. Until now they haven't faced competition on the US market. Biologics and biosimilars are produced by living organisms, which may include bacteria, yeast, animals, or plants. The active ingredient in Neupogen, like Zarxio, is made by *Escherichia coli* bacteria that have been genetically modified to produce granulocyte colony-stimulating factor, a protein that plays an important role in blood cell health.

The road to the US market has been slow. The US government first established a regulatory pathway for biosimilars with the Biologics Price Competition and Innovation Act (BPCIA), which became law in 2010 as part of the Patient Protection and Affordable Care Act. "The intent of the BPCIA is to provide patients with access to lower cost, safe and effective biological products," says molecular biologist Leah Christl, an associate director for therapeutic biologics in the FDA's Office of New Drugs. The European Union finalized a pathway for the approval of the drugs in 2004 and approved its first in 2006. Japan approved its first drug in 2009; South Korea followed in 2012.

Fair Trade

Biosimilars are not automatically interchangeable at the pharmacy counter and require a separate prescription per FDA

regulations. The agency has not yet released guidance on how manufacturers can establish interchangeability, a deficit pointed out by Elizabeth Warren, US Senator of Massachusetts, at a Senate Subcommittee hearing on September 17, 2015. "It has now been five years since Congress authorized the biosimilars pathway, but so far the FDA hasn't even produced a draft guidance describing the standard for an interchangeable biosimilar," said Warren. "It is time now to get this done. The longer it takes you to set the rules, the longer patients will be stuck with paying only one very expensive option to meet their medical needs."

Janet Woodcock, director of the FDA's Center for Drug Evaluation and Research, responded at the hearing that although interchangeability is an important next step, the agency has been focused on verifying the science. "The most important thing we had to do was set a scientific framework that was bulletproof, that will earn the trust of the community and will actually work to provide biosimilars that are safe and effective and have the same properties as the innovator," Woodcock said.

Challenges Ahead

Biologics are expensive to develop and manufacture, and often require costly cold storage. Fine-tuning the development process of a given drug may require seven or eight years, says Richard Markus, the Vice President of Biosimilars Global Development at Amgen. "It's different from making small-molecule drugs," he says. "Every manufacturer of a biologic or biosimilar has to start with a new cell line. The technical challenge really is, can you develop that protein with a new [process] and create a high-quality match?" Amgen, like other large pharmaceutical companies, is actively pursuing its own line of biosimilars. These include ABP980, a biosimilar for Genentech's targeted biologic drug Herceptin, used to treat patients whose breast cancer cells overexpress a receptor called HER2.

At the September hearing, the FDA's Woodcock noted that 57 biosimilar products, based on 16 reference products, were in development. Mulcahy expects to see a few of those to be approved in the next one to five years, including some that are already approved in Europe.

"I think there will be a rocky road for the first few biosimilars as they navigate these new processes," he says. "Once we have 5 or 10 approved, and we're a few years out from now, things will settle down." At that point, he says, it should be possible to assess their influence on health care spending.

1 Grabowski H, Guha R, Salgado M (2014) Biosimilar competition: Lessons from Europe. *Nat Rev Drug Discov* 13(2): 99–100.

2 Mulcahy AW, Predmore Z, Mattke S (2014) *The Cost Savings Potential of Biosimilar Drugs in the United States.* (Rand Corporation, Santa Monica, CA).