HealthAffairs

PRESCRIPTION DRUG PRICING

HEALTH POLICY BRIEF SERIES
JULY 2017 | 3

BIOSIMILARS

Follow-on products to innovative brand-name biologic medicines may lower overall drug spending by creating price competition.

The recent rise of biologic medicines has produced a wave of new therapies. Biologics include a range of products, including vaccines, recombinant therapeutic proteins, blood and blood components, gene therapies, and others. These new medicines—most of which are complex molecules more difficult to produce than traditional, small-molecule drugs—are important medical advances, but they have driven prescription drug spending higher overall. The hope is that biosimilars—follow-on products to innovative branded biologics—will lower overall drug spending by creating price competition for those biologics in the same way generic drugs compete with traditional branded medicines. However, unlike generic drugs, where substitution of the generic for the brand name is embedded in practice through state laws and health plan policies, the launch of a biosimilar does not trigger pharmacist substitution of the biosimilar for the original biologic—the primary mechanism that creates price competition for small-molecule drugs. The impact of biosimilar development on pricing may therefore be much less substantial than the impact of generic drugs—at least for the foreseeable future.

Background

The 1984 generic drug law, known as the Hatch-Waxman Act, plays an important role in promoting price competition once brand-name drugs lose patent protection. The law, however, does not apply to biologic medicines, which account for a growing proportion of the top-selling prescription drugs in the US. In 1984 the biotechnology sector was in its infancy, and the primary medicines regulated as biologics were vaccines or drugs derived from human blood (such as hemophilia clotting factors). By the 2000s, however, biologic medicines were increasingly common as therapeutics. Congress recognized that a process to copy those therapies would be more complicated than the process for small-molecule drugs, which are structurally simpler.

Under the Biologics Price Competition and Innovation Act (BPCIA) of 2010 (part of the Affordable Care Act), Congress created an abbreviated Food and Drug Administration (FDA) approval pathway for "biosimilar drugs"—versions of biologics made by manufacturers other than the original innovator. The goal was to open up price competition for biologic therapies after their patents expired. While the approach is patterned on the generic drug process, the new pathway reflects the greater complexity of the underlying products and the associated

WITH SUPPORT FROM:

The Commonwealth Fund

Drug Pricing Lab
Memorial Sloan Kettering

challenge of ensuring that the safety and efficacy of "copies" match that of the innovator drug.

The chemical and molecular makeup of biologics is critical to understanding the differences between the generic and biosimilar regulatory models. Generics are chemically equivalent and bioequivalent—that is, the drugs have the same active ingredient and are absorbed in the patient's bloodstream at the same rate as the branded small-molecule drugs they copy. Biologics are significantly larger, more complex molecules, which makes them scientifically difficult to fully replicate. As a result, the biosimilar pathway requires functional or clinical equivalence, rather than chemical equivalence.

The impact of the Hatch-Waxman Act underscores the potential, future impact of the biosimilar drug pathway. According to a Congressional Budget Office study, generics made up about 20 percent of the US prescription drug market at the time of the act's passage but now represent almost 90 percent of that market. According to the FDA, consumers pay roughly 80–85 percent less for a generic compared to the brand. No one expected the biosimilar pathway to have that level of impact right away. The FDA, in particular, has moved cautiously in the use of the pathway, with an emphasis on safety. In addition, ongoing litigation has delayed or blocked market entry for the first wave of products born out of the BPCIA.

There have been five biosimilars approved (with two launched commercially) since the BPCIA was enacted (Exhibit 1). These products will likely offer competition more akin to "'me too" brands (chemically similar, but not identical, drugs that treat the same disease with no demonstrably different properties) than to generics.

The Biosimilar Approval Process

There are several important elements in the biosimilar approval process.

DIFFERENT STANDARDS OF APPROVAL

The biosimilar pathway requires the FDA to approve therapies based on a different standard than it uses for new drugs (including biologics), which generally requires human trials to prove safety and efficacy. The standard is also different from the one used by the FDA for approval of generics, which usually requires a small human study measuring blood levels of the active ingredient compared to the brand, to prove "bioequivalence." Short comparative studies of the generic drug's activity in healthy volunteers typically suffice for FDA approval.

Unlike generic drugs, biosimilars do not have to meet a standard of bioequivalence to the reference product. Instead, the legal standard laid out in FDA guidance is that biosimilars must be "highly similar" to the reference product, notwithstanding minor differences in clinically inactive components. Furthermore, there may be no clinically meaningful differences between the biosimilar and reference products in terms of safety, purity, and potency. The FDA applies a "stepwise approach" to reaching that standard, with early characterization of the biosimilar through analytical and animal studies and (usually) at least one clinical study. At every step, the biosimilar sponsor must analyze the extent of any residual uncertainty about the biosimilarity of the product to the reference product and determine steps to resolve it.

EXHIBIT 1

FDA-Approved Biosimilars

Biosimilar	Reference Innovator	Approved	Launched
Sandoz's Zarxio (filgrastim-sndz)	Amgen's Neupogen	2015	Yes
Celltrion's Inflectra (infliximab-dyyb)	Johnson & Johnson's Remicade	2016	Yes
Sandoz's Erelzi (etanercept-szzs)	Amgen's Enbrel	2016	No
Amgen's Amjevita (adalimumab-atto)	AbbVie's Humira	2016	No
Samsun Bioepis's Renflexis (infliximab-abda)	Johnson & Johnson's Remicade	2017	No

SOURCE Prevision Policy LLC; FDA and company press releases.

"INTERCHANGEABILITY" AND SUBSTITUTION

When bioequivalent generic drugs are approved by the FDA, state laws permit (and usually encourage) pharmacists to substitute generic for brand-name products without contacting the physician. This is a critical reason that prices for pharmaceuticals drop rapidly after generic entry.

An FDA-approved biosimilar, however, is not automatically deemed interchangeable with the brand-name biologic and cannot be substituted without physician approval. Interchangeability requires a second determination above the finding that it is "highly similar" to the reference product. FDA's draft standard for interchangeability indicates that the risk of "switching between use of the [biosimilar] product and its reference product is not greater than the risk of using the reference product without such alternation or switch." There have been, to date, no biosimilars deemed interchangeable with innovator biologics. In addition, many states have passed laws carving out biosimilars from drug substitution laws, essentially blocking pharmacist substitution even if the FDA deems a biosimilar interchangeable.

"Many states have passed laws carving out biosimilars from drug substitution laws."

Another challenge for substitutability is the FDA's policy that biosimilars carry a unique nonproprietary name compared to the branded product, so regulators, physicians, pharmacists, and consumers can distinguish between the two. Specifically, manufacturers must apply a four-letter "nonsense" suffix to the nonproprietary name of biologics. For example, for the biologic adalimumab (sold as brand-name Humira), the biosimilar will be called "adalimumab-atto." According to the FDA, "Distinguishing suffixes should help minimize inadvertent substitution of any such products that have not been determined to be interchangeable."

TWELVE-YEAR MARKET EXCLUSIVITY

Protecting incentives for development of new biologics was a high priority for legislators—and a subject of considerable debate—when Congress designed the biosimilar pathway. The new law precludes approval of a biosimilar application until twelve years after the date on which the reference product was first licensed. That is substantially longer than the five-year protection (four years if a patent is challenged) for brand-name pharmaceuticals under the Hatch-Waxman Act.

THE "PATENT DANCE" CAN CAUSE DELAYS

The biosimilar pathway includes a unique process for resolving patent disputes prior to the potential approval of a biosimilar application. In what is referred to as the "patent dance," biosimilar and reference-product sponsors must exchange intellectual property information and work through patent disputes according to a schedule. In theory, the process assures smoother, more predictable entry for biosimilar products than has been the case with the Hatch-Waxman generic drug patent challenge system. However, the ground rules for the patent dance have already generated litigation that has been brought to the Supreme Court, which ruled in June 2017, in *Sandoz Inc. v. Amgen Inc.*, that the patent dance is optional under federal law.

Key Questions For Drug Pricing And Coverage Policy

There are several outstanding questions about how or whether the biosimilar pathway should affect drug prices and coverage policy.

UNCERTAIN COMPETITIVE IMPACTS

It is unclear whether more biosimilars will lead to lower prices. Prior experience with generic drugs suggests that prices come down to about half the original price when there are at least two competitors, and to as low as one-third when there are a half-dozen fully interchangeable, competing products. It remains an open question whether a similar level of price competition will emerge for biologics. Biosimilar developers argue that without interchangeability, there will likely never be such price reductions for biologics. The first

biosimilars (Exhibit 1) were launched commercially in the US at modest discounts (in the range of 15–20 percent) from the reference product. For the foreseeable future, given the small number of biosimilars approved, the competitive landscape for biologics won't likely differ from that of a brand-versus-brand market.

THE ROLE OF MEDICARE PART B

Some stakeholders believe that Medicare payment policy should address the cost of biologics more directly. The biosimilar law includes provisions related to Medicare Part B, which covers physician-administered drugs and is an important market for many biologics used for cancer and rheumatology. Medicare is prohibited from applying the same payment to a biosimilar and an innovator drug. Instead, the program must have separate payment codes for the biosimilar and the innovator, albeit with a formula intended to minimize incentives for physicians to choose the brand over the biosimilar (physician are paid a percentage of the brand price, not the biosimilar price, if the biosimilar is prescribed). In theory, combining the brand and biosimilar products under a single payment code would do more to encourage price competition. The provider would receive the same reimbursement no matter which therapy is used and thus would have an incentive to choose the lowest-cost agent.

SUBSTITUTION WITHOUT INTERCHANGEABILITY?

The initial FDA approvals have been for noninterchangeable biosimilars, which typically means that the prescriber will have to select the biosimilar for it to be dispensed. There have been some efforts to revise state pharmacy laws to treat biosimilars as interchangeable for substitution purposes, but those have been largely unsuccessful and are opposed by the FDA. However, physicians are now increasingly accountable for drug costs under capitated or bundled payment arrangements, particularly for conditions (such as cancer) in which biologics are used. Payers may therefore be able to encourage providers' adoption of biosimilars, even without interchangeability.

The Centers for Medicare and Medicaid Services has also supported policies to promote biosimilar adoption by Medicaid and Medicare Part D, including a policy allowing Part D plans to limit formularies to include only the biosimilar when one is available.

HealthAffairs

Health Policy Briefs are produced under a partnership of *Health Affairs* with the generous support of the Commonwealth Fund and Memorial Sloan Kettering Cancer Center. Text highlighted in blue is hyperlinked to outside sources in the online version of this brief.

Written by **Ramsey Baghdadi**, Prevision Policy LLC. Editorial review by **Aaron Kesselheim**, Harvard Medical School and Brigham and Women's Hospital; **Gail R. Wilensky**, Project HOPE; **Laura Tollen**, consulting editor, *Health Affairs*

Cite as: "Health Policy Brief: Biosimilars," Health Affairs, July 21, 2017. DOI: 10.1377/hpb2017.4

7500 Old Georgetown Road, Suite 600 | Bethesda, Maryland 20814-6133 USA |