Emerging Competition Issues in Biologics

By Sara Champion, Rahul Guha, and Maria Salgado
Cornerstone Research

Background

Biologic drugs are “protein-based and derived from living matter or manufactured in living cells using recombinant DNA biotechnologies.” Biologic drugs are much larger and more complex molecules than traditional pharmaceuticals, and are often injected or infused. The Biologics Price Competition and Innovation Act of 2009 (“BPCI Act”), which was signed into law on March 23, 2010, established an abbreviated approval process for drugs demonstrated to be highly similar (i.e., biosimilar) or interchangeable with the reference biologic approved by the Food and Drug Administration (“FDA”). In this article, we analyze the competition issues that are likely to be relevant for biologics and biosimilars as a result of the passage of the BPCI Act.

Biologic drugs account for a large portion of top-selling drugs in the pharmaceutical pipeline. For example, in 2010, U.S. sales of biologics exceeded $30 billion, and seven biologics were among the top 20 selling pharmaceuticals. Biologics also represent over 40 percent of the drugs in each of the preclinical, Phase I, Phase II, and Phase III trial stages. It is no wonder that the passage of the BPCI Act and follow on FDA guidance have been watched so closely.

Competition Issues in Biologics

Competition between biosimilars and biologics will likely be less severe than generic competition for small-molecule drugs. Three major factors contribute to this: (1) biosimilars are not chemically identical to their reference products; (2) a biosimilar cannot be approved by the FDA until the reference biologic has been on the market for 12 years; and (3) the reimbursement rules for biologics and biosimilars do not encourage biosimilar use. We discuss these three factors in detail below, as well as their implications for competition between biosimilars and biologics.

The regulatory process recognizes that, unlike small-molecule generics, biosimilars are not chemically identical to their reference products. This has several implications for competition between biologics and biosimilars. First, because biosimilars are not exact replicas of the reference biologic, they do not compete with the reference biologic solely on price, but also on quality. Second, the FDA will generally require additional animal and clinical testing from the biosimilar applicant (when compared to what is required for small-molecule drugs) to ensure that the drug can be considered a biosimilar. The higher costs of FDA approval increase the barriers to entry for biosimilars, resulting in fewer expected biosimilar competitors for each reference biologic when compared to small-molecule generics. Specifically, the expected cost to develop and approve a biosimilar drug is $100-$200 million, with a time to market of 8-10 years. In contrast, small-molecule generics cost $1-$5 million and take 3-5 years to develop. Lastly, most biosimilars will not be considered interchangeable with their reference products because of the difficulties in making them sufficiently similar to their reference products in a way that satisfies the stricter safety and efficacy standards that must be met for interchangeability to hold. As a result, biosimilars will likely not be automatically substituted for biologics at the pharmacy, as is possible in most states for small-molecule generics. Indeed, Virginia recently passed a law that allows pharmacists to dispense a biosimilar product instead of a reference biologic only when the biosimilar is considered interchangeable by the FDA, and only if the patient and provider do not oppose the substitution. North Dakota, Oregon, and Utah have also passed legislation which places restrictions on the substitution of biosimilars for biologics at the pharmacy. As a result, the market share loss experienced by the reference biologic upon entry of a biosimilar competitor will likely be significantly lower than what is observed for small-molecule drugs. The lack of pharmacy substitution will require biosimilar companies to differentiate their products through promotions and marketing, similar to what branded-drug companies do for their products.

Another important feature of the regulatory process established by the BPCI Act is that the biosimilar cannot be approved by the FDA until the reference biologic has been on the market for 12 years. This means that biosimilar drugs can only enter the market towards the end of the lifecycle of the reference biologic drug. For small-molecule drugs, assuming no patent protection, generics are allowed to enter after the branded drug has been on the market for five years. The result of this is that biosimilar competitors can earn profits over a fewer number of years (when compared to a situation of a shorter exclusivity period for the reference product), and less competition from biosimilars can be expected as a result.

---

5 FTC Report, supra note 2, at 14.
6 Id. at iii.
Finally, the BPCI Act established the reimbursement rules for biologics and biosimilars. Because these products are typically injected or infused, many of them are covered under Medicare Part B. The BPCI Act set the reimbursement for biologics at 106 percent of the biologic drug’s average sales price (“ASP”), while the biosimilar reimbursement was set at 100 percent of the biosimilar drug’s ASP plus 6 percent of the reference biologic drug’s ASP.\(^\text{12}\) In other words, the amount of reimbursement beyond the ASP is the same regardless of whether the biologic or the biosimilar is reimbursed, and always covers the cost of the drug. As such, this reimbursement rule does not encourage the use of biosimilars. In contrast, for small-molecule drugs, the Medicare Part B reimbursement is set at 106 percent of the combined ASP of the brand and generics.\(^\text{13}\) Because branded drugs cost more than generics, 106 percent of the combined ASP may turn out to be lower than the provider’s cost for the drug (e.g., if the volume of generics on the market is high). As such, providers will have an incentive to prescribe the generic drug, thus rapidly increasing generic-drug use. Such incentives to prescribe the lower-cost drug are not present for biosimilars.

Combined, these factors indicate that both the price discounts from biosimilars and the biosimilar penetration will be lower than what is observed for small-molecule generics. The number of biosimilar entrants for each biologic reference product is also expected to be lower.

To understand how biosimilar competition may evolve in the U.S. as a result of the BPCI Act, it is helpful to understand how competition between biologics and biosimilar-like drugs (i.e., drugs that are not biosimilars but have some features of biosimilar drugs) has evolved.

The first example is in the human growth hormone market upon the entry of Sandoz’s Omnitrope, a biosimilar-like drug that was not considered interchangeable with its reference biologic, Pfizer’s Genotropin. When Omnitrope launched in 2007, the human growth hormone market already had several branded products, and competition occurred on price, as well as delivery device (cartridge and pen system).\(^\text{14}\) After the launch of Omnitrope, Genotropin maintained a market share of over 80 percent of the combined Genotropin-Omnitrope sales (measured in dollars or units) through 2011.\(^\text{15}\) Omnitrope was not able to capture significant market share despite launching an improved pen cartridge delivery system in 2008. The competition between Omnitrope and Genotropin has been much more similar to brand-to-brand competition in the small-molecule drug market than typical generic competition. It is also noteworthy that the formulary placement of Omnitrope and Gentropin in the U.S. resembles more what is observed for two branded small-molecule drugs in that it does not encourage use of Omnitrope.\(^\text{16}\)

---


\(^{13}\) MEDICARE PAYMENT ADVISORY COMMISSION, REPORT TO THE CONGRESS: IMPROVING INCENTIVES IN THE MEDICARE PROGRAM (2009), at 115-117.

\(^{14}\) FTC Report, supra note 2, at 21-22.

\(^{15}\) Analysis based on IMS Health data (2000-2012) maintained by the authors.

\(^{16}\) Analysis based on Fingertip Formulary data (Oct. 2011) maintained by the authors.
Genotropin continued to be preferred on most health plan formularies over Omnitrope.

In contrast, the competition in the U.S. between Lovenox and enoxaparin, a biosimilar-like product approved through an Abbreviated New Drug Application (“ANDA”) filing in July 2010, is very similar to what is typically observed with small-molecule generics. Enoxaparin was approved through an ANDA and, therefore, substitution at the pharmacy level is permitted. Lovenox experienced steady growth from 2000-2009, but experienced a marked drop in its sales after the introduction of enoxaparin in the fourth quarter of 2010. Enoxaparin was able to capture over 50 percent of the combined Lovenox- enoxaparin market (in dollars or units) in its first year on the market. The formulary placement of Lovenox and enoxaparin incentivized the use of enoxaparin over Lovenox, much like formulary placement of generic and brand-name small-molecule drugs. In sum, competition between Lovenox and enoxaparin resembles brand-to-generic competition for small-molecule drugs and provides insights into future biosimilar drug penetration where interchangeability is demonstrated and pharmacy substitution is allowed.

In addition to the above experiences in the U.S., the biosimilar experience in the European Union, which has had a pathway for biosimilars since 2005, may provide insight into what will happen in the U.S. once biosimilar entry occurs under BPCI Act. Germany, in particular, may be an especially good comparable to the U.S. because of the similarities between the two healthcare systems. Specifically, like in the U.S., health insurance plans in Germany influence prescribing decisions, and patients pay a share of drug costs under some circumstances.

Germany has experienced biosimilar entry for three reference biologic drugs: Amgen’s Eprex (epoetin alfa), marketed as Epogen/Procrit in the United States; Neupogen (filgrastim); and Genotropin/Humatrope (somatropin). The biosimilar share of the reference product market has been varied. Biosimilars for Eprex captured over 60 percent of the epoetin alfa market in 2011 (measured in daily doses), and biosimilars for Neupogen captured approximately 45 percent of the filgrastim market in that year. In contrast, biosimilars for Genotropin and Humatrope captured less than 10 percent of the market for human growth hormone products in 2011. Differences in the uptake of biosimilars across different products may be due to several factors, including differences between the biosimilars and their reference products (for example, that cause providers to be concerned about the comparability of the drugs in terms of safety, efficacy, and/or ease of use), or differences in the strategies employed by the biosimilar manufacturers to gain share (e.g., marketing or price discounts).

18 Analysis using IMS Health data (2000-2012) maintained by the authors.
19 Id.
20 Analysis using Fingertip Formulary data (Oct. 2011) maintained by the authors.
21 Biosimilars Approved and Marketed in Germany, Generics and Biosimilars Initiative (Nov. 23, 2012), available at http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-and-marketed-in-Germany/(highlight)/the%20federal%20institute%20for%20drugs%20and%20medical%20devices%20is%20responsible.
22 Analysis using IMS Health data (2009-2011) maintained by the authors.
23 Id.
Even if biosimilars end up gaining a large share of sales from the reference product in the U.S., their share of overall patient treatment may be limited in the face of incremental technological change that includes patients switching to next-generation products. This happened for Eprex in Europe when Amgen introduced a second-generation long-acting product called Aranesp (darbepoetin), which so far has not experienced biosimilar competition. In Germany, the biosimilar shares (measured in daily doses) among both the first and second generation products (Eprex and Aranesp) were much lower than the biosimilar shares among Eprex only. These lower biosimilar shares reflect the fact that the second-generation longer acting formulation, Aranesp (darbepoetin), has surpassed Eprex as the market leader in this class of drugs. A similar effect was observed for Neupogen, with second-generation product Neulasta largely taking over the market for these drugs.

**Conclusion**

In sum, competition between biologics and biosimilars under the BPCI Act will be impacted by many factors, and it appears that competition will not be as fierce as what is observed between brand-name drugs and small-molecule generic drugs. The entry of biosimilar-like drugs in the U.S. and biosimilars in Europe can offer some insight into how competition will evolve and into what factors will be most important in determining the level of competition.

---

24 This is also a common aspect of competition between brand and generic small molecule drugs.

25 Analysis using IMS Health data (2009-2011) maintained by the authors.

26 Id.