Introduction

The U.S. Food and Drug Administration ("FDA") licensed the first biosimilar therapeutic, Sandoz’s Zarxio®, the biosimilar version of Amgen’s anti-cancer biologic Neupogen®, on March 6, 2015. This event marks an important milestone in the evolution of the regulatory approval process for biosimilars in the United States, a process almost six years in the making. While the past year has seen an accelerated pace of that process, a number of salient issues remain open. This article presents a brief summary of the past year and an outline of what to expect in the future.

A biological product is a therapy used to treat a disease or health condition, and includes vaccines, blood and blood components, gene therapies, tissues, and proteins. Biologics differ from traditional “small molecule” drugs in several ways. First, whereas drugs are made through chemical processes, biologics are made through biological processes. Second, biologics are typically larger and more complex than small molecule prescription drugs. By comparison, biologics are often difficult to make, characterize, and compare to one another, and are relatively expensive to develop. The time and cost to develop, produce, and obtain FDA approval for biologics have contributed to the high prices and limited patient access to these products.

Congress enacted the Biologics Price Competition and Innovation Act ("BPCIA") as a provision of the Patient Protection and Affordable Care Act in 2010. The BPCIA amended the Public Health Service Act ("PHS Act") to establish an abbreviated route to FDA licensure for biologics shown to possess the requisite level of similarity to an existing FDA-licensed reference product. The BPCIA is intended to increase access to lower-cost biologics, much like what the Hatch-Waxman Act created for generic small molecule drugs.

Section 351(k) of the BPCIA provides two levels of similarity on which sponsors may seek regulatory approval. At the first level, a biologic may be demonstrated to be biosimilar to the reference product if the products are "highly similar," notwithstanding minor differences in clinically inactive components, and that there are "no clinically meaningful differences" between the products in terms of safety, purity, and potency. Unlike generic small molecule drugs, pharmacists may not unilaterally substitute a biosimilar for its reference product. At the second level, a biosimilar may be found interchangeable with the reference product if it is “expected to produce the same clinical result” and the risk in terms of safety or efficacy resulting from switching between them is no greater than that of using the reference product. Interchangeable biologics are eligible for automatic substitution for their reference biologic by pharmacists.
Although many fundamental issues concerning the BPCIA remain unresolved, and FDA has been slow to provide guidance to industry regarding the biosimilars pathway, several guidances have provided some detail for manufacturers. Other issues remain unsettled, including how biosimilars will be named and whether and how interchangeable biosimilars may be substituted for reference biologics. FDA’s recent licensure of the first biosimilar for use in the United States likely will serve as a test case for further development of many of these issues.

Substitution

Whether a biologic is found to be a biosimilar, and if so whether the biosimilar is found to be interchangeable with a reference biologic, is a determination made by FDA under federal law. However, as with generic small molecule drugs, whether an interchangeable biosimilar may be substituted for the reference or brand-name biologic is a matter of state law, in particular state laws governing the practices of pharmacists and physicians. Since the passage of the BPCIA, a growing number of states have passed laws addressing pharmacist substitution of an interchangeable biosimilar. Recent statistics showed that eight states (Delaware, Florida, Indiana, North Dakota, Oregon, Utah, and Virginia) had enacted statutes relating to the substitution of biosimilars, fourteen states (Arkansas, Arizona, California, Colorado, Georgia, Illinois, Maryland, Michigan, Mississippi, Nevada, Pennsylvania, Texas, Vermont, and Washington) had proposed bills that were voted down or vetoed, and one state (New Jersey) had such a bill pending.\(^1\)

The provisions of these bills and laws have varied, with some requiring prior physician approval before substitution and others requiring notice to the physician after substitution. Most have allowed the prescriber to block substitution by writing “dispense as written,” while others require the prescriber affirmatively to write “may substitute” to allow substitution. Not surprisingly, different stakeholders and industry groups have promoted different approaches, and the various state laws to date ran the gamut of these different approaches.

In December 2014, the industry trade groups Generic Pharmaceutical Association (“GPhA”) and the Biotechnology Industry Organization (“BIO”) reached a compromise on this issue. These groups had previously disagreed over the proposed requirement that pharmacists notify prescribing physicians before making a substitution, but in the recent compromise the groups instead suggested requiring pharmacists to communicate information about the substitution to physicians after the fact. As we move forward in 2015, it remains to be seen what effect this compromise will have on emerging state laws. A new biosimilars bill cleared the Georgia Senate Health and Human Services Committee on February 12, 2015. Consistent with the compromise recently reached by industry groups, the Georgia bill requires notification of substitution to the prescriber after the fact.\(^2\)


To date, these substitution laws remain abstract because they will only apply to a biosimilar that is further found to be interchangeable, and such finding of interchangeability is likely years away.

**Naming**

The question of how to name biosimilars has been hotly contested among several stakeholders due to its potential to impact how the marketplace receives biologics. Some stakeholders argue that the naming scheme for biosimilars should follow that of small molecule drugs. Generic small molecules are required to be bioequivalent, and thus a generic small molecule drug necessarily shares the non-proprietary name with the reference listed drug. For example, Motrin® is the brand name for ibuprofen. Generic versions of the drug all use the non-proprietary name ibuprofen. But other stakeholders disagree, arguing that the manufacturing process for biologics is much more complex, and the final protein structures of biologics are susceptible to any number of differences depending on the manufacturing process, equipment, location, and conditions. Even minor differences in structure can have a dramatic impact on how the molecule behaves clinically. As discussed in more detail below, FDA has recognized that because of these factors a biosimilar will not be identical to the original biologic products, and has issued draft guidance that recognizes four levels of similarity: not similar, similar, highly similar, and highly similar with fingerprint-like similarity. Thus, the question whether biosimilar can justifiably use the same non-proprietary name as a reference biologic to which they are to some degree – one of at least four degrees – similar is debatable.

On the one hand, the biologics industry, through groups such as the Alliance for Safe Biologic Medicines, has argued for unique non-proprietary names for biosimilars on the basis that having different names promotes pharmacovigilance, while having biologics of the same name would incorrectly infer interchangeability. Patient groups such as the National Organization for Rare Diseases (“NORD”) have agreed, noting that unique names for non-identical compounds would reduce confusion. On the other hand, the generics industry, through groups such as GPhA, has argued that biosimilars be given the same non-propriety name on the basis that biosimilars have been in use in the European Union for years without major safety issues. In addition, the World Health Organization (“WHO”), which coordinates the International Nonproprietary Name (“INN”) system, has proposed a “biological qualifier”

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4 A. Gaffney, Regulatory Affairs Professionals Society, “Pharmacovigilance Concerns Lead Group to Call for Unique Names for Biosimilar” (September 17, 2012) (http://www.raps.org/regulatoryDetail.aspx?id=7527).


system that would preserve the reference product’s original name but would require biosimilars to add a unique code onto that name, and has invited comment on its proposal.7

As matters stand with FDA, GPhA filed a Citizen Petition requesting FDA to “implement the INN naming policy equally to all biologics” and to require “all biologics approved under the Section 351(k) pathway . . . share the same INN as the RPP [reference protein product].”8 In its January 31, 2014 response, BIO stated “a system that assigns the same name to products that are similar, but not the same, would create confusion for physicians and patients, hinder effective pharmacovigilance, and could jeopardize patient safety,” and that “[t]hus, BIO supports the development of a system under which nonproprietary names of biological products that are similar to each other in structure and function are distinguishable, but morphologically related, and which both prescribers and patients can easily recognize, remember, and report accurately.”9

FDA had previously indicated that it would prefer to issue its anticipated biosimilars naming guidance before approving any biosimilars, but in light of the Agency’s first recent biosimilar approval, this apparently was not the case, despite urging from Congress to issue the guidance.10 It is likely that 2015 will be a pivotal year in this ongoing debate.

New FDA Guidances

FDA released three draft guidances in February 2012 and a fourth draft guidance in March 2013. Collectively, these previous draft guidances provided relatively general principles concerning the biosimilars application process. The year 2014 brought two more draft guidances which added a level of detail not previously provided. Additional guidances are expected on topics including interchangeability, labeling, and exclusivity. Most recently, in April 2015 FDA released three guidances finalizing the 2012 draft guidances, each intended to clarify the scientific and regulatory considerations for drug companies developing biosimilars.

The May 2014 draft guidance, Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, is intended to assist biological product sponsors with the design and use of clinical pharmacology studies to support a showing that a proposed therapeutic biological product is “biosimilar” to its reference product under the BPCIA. As the most detailed guidance yet on evidence needed to support biosimilarity, the draft guidance sought to further clarify the cost of bringing a biosimilar to market.

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Specifically, the guidance covered overarching concepts related to clinical pharmacology testing for biosimilars, approaches for developing the appropriate clinical pharmacology database, and the utility of modeling and simulation for designing clinical trials. In addition, the draft guidance introduced FDA’s expectations for bridging data from products marketed outside of the United States and established key topics about which sponsors should meet with FDA early on in the biosimilar development process. The encouragement of early meetings with FDA echoed the Agency’s “stepwise” approach to biosimilar approval, suggested in earlier draft guidances, which allows a sponsor to undertake research, identify areas of uncertainty, and then tailor future research to address those areas of uncertainty. Finally, the May 2014 draft guidance introduced four categories of similarity—not similar, similar, highly similar, and highly similar with fingerprint-like similarity—that will affect the extent to which further study is needed to establish biosimilarity.

The August 2014 biosimilar draft guidance, Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act, is intended to help biological product sponsors and applicants in submitting appropriate information to FDA to enable a regulatory determination of the “first licensure” date of a reference biological product under section 351(k)(7)(C) of the PHS Act. Under section 351(k) of the PHS Act, an application for a biosimilar or interchangeable biologic may not be submitted to FDA until four years after, or approved until 12 years after, first licensure of the reference biologic. These periods are respectively referred to as periods of “data exclusivity” and “market exclusivity.” Additional exclusivities may also apply, such as pediatric or orphan drug exclusivities.

The determination of the date of first licensure of a reference biological product is critical because it effectively decides the product’s eligibility for various exclusivities and the lengths of those exclusivity periods. But determining this date is far from simple. Generally, the date of first licensure of a reference product submitted under section 351(a) will be the initial date FDA licensed the product. But section 351(k)(7)(C) excludes from this determination the date of licensure for (1) a supplement for to the reference product or (2) an application by the same sponsor of the reference product for (a) a non-structural modification resulting in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device, or strength, or (b) a structural modification that does not alter safety, purity, or potency.

According to FDA, “because of these exclusions, for each product licensed under section 351(a) of the PHS Act that may serve as a reference product for a biosimilar application, FDA must make a determination regarding the date of first licensure.” In its draft guidance, FDA explains how it intends to make these determinations, including a consideration of whether the product has been structurally modified, and whether there has been a change in safety, purity, or potency, and provides concrete examples as illustrations of its intended approach. The draft guidance also provides suggested information sponsors should include in their 351(a) applications.

FDA finalized three draft guidances in April 2015 addressing scientific and regulatory considerations in developing biosimilars. The first 2015 final guidance, Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, is directed at proposed therapeutic protein products, rather than all biologics, although some of the principles in the guidance may apply more widely to all biosimilar products. The guidance begins by advising
sponsors to consider the complexities of protein products when designing programs to demonstrate biosimilarity, and provides specific scientific and manufacturing considerations related to the unique and complex nature of protein products, such as differences in structure. The guidance discusses a “stepwise” approach sponsors should use in developing the evidence needed to support biosimilarity, and advises sponsors that FDA will use a totality-of-the-evidence approach to assess a demonstration of biosimilarity. The guidance specifies that “a sponsor may be able to demonstrate biosimilarity even though there are formulation or minor structural differences, provided that the sponsor provides sufficient data and information demonstrating that the differences are not clinically meaningful and the proposed product otherwise meets the statutory criteria for biosimilarity.” Finally, the guidance emphasizes the importance of postmarketing safety considerations and recommends that prospective sponsors meet with FDA to present their plans and receive agency feedback.

The second 2015 final guidance, *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product*, focuses on scientific and technical information for the chemistry, manufacturing, and controls (“CMC”) section of a biosimilar application. Like the first 2015 guidance, this guidance specifically applies to therapeutic protein products, but contains principles that could also guide development of other protein products. The guidance begins by cautioning that “current analytical methodology may not be able to detect or characterize all relevant structural and functional differences between the two protein products,” and suggests a “thorough understanding of each analytical method's limitations will be critical to a sponsor's successful identification of residual uncertainties and, in turn, to the design of subsequent testing.” The guidance also discusses the importance of comparative physicochemical and functional studies, issues related to heterogeneous primary structures, the impact of a protein’s three-dimensional conformation to biological function, and the role of non-U.S.-licensed products. Finally, the guidance identifies factors to consider in assessing whether products are highly similar, including manufacturing process, physicochemical properties, functional activities, receptor binding, impurities, reference standards, and stability.

The third 2015 final guidance, *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009*, provides answers to common questions regarding FDA’s interpretation of the BPCIA, and is divided into three categories. “Biosimilarity or Interchangeability” discusses permissible differences between biosimilars and their reference products and addresses whether a sponsor can use comparative data with a non-U.S.-licensed product to demonstrate biosimilarity. “Provisions Related to Requirement to Submit a BLA for a Biological Product” addresses how the category of proteins meets the amended definition of a “biological product” and how “product class” is defined for purposes of demonstrating whether an application for a biologic may be submitted under the Food, Drug, and Cosmetic Act during the transition period. Finally, “Exclusivity” addresses a single question related to orphan exclusivity for reference products.


The BPCIA contains a procedure for resolution of patent disputes which is similar in concept to Hatch-Waxman litigation for small-molecule drugs, but differs in several critical ways. The BPCIA has been dubbed the “Patent Dance” by commentators because of its complexity.
At the outset, the applicant provides a copy of its Biologics License Application (“BLA”) to the reference sponsor within 20 days after FDA accepts it for review. Then, within 60 days the reference sponsor must identify patents on which an infringement claim could reasonably be asserted and which patents it would be willing to license. The parties must then negotiate the claims, and if after fifteen days they have not reached an agreement, then the reference product sponsor may then bring suit for patent infringement.

In addition to disclosing the BLA at the outset, the applicant must provide notice of commercial marketing to the reference product sponsor at least 180 days before launch of the biosimilar. The reference sponsor may seek a preliminary injunction prohibiting the applicant from making or selling the biosimilar until a court decides validity, infringement, or enforcement of the patents.

While this process is ongoing, both parties are generally prohibited from bringing declaratory judgment actions. Failure by the applicant to complete certain actions required by the BPCIA provides the reference sponsor with the right to bring a declaratory judgment action. The BPCIA also contains provisions for the handling of confidential information, which are applicable unless the parties agree to other arrangements.

Court Decisions in 2014

The Patent Dance procedure has been described as “cumbersome,” and the requirement of turning over confidential information to a competitor has made the procedure unattractive compared to traditional declaratory judgment proceedings. It is thus unsurprising that the first cases involving the BPCIA have addressed procedural matters at whose core seems to lie the question whether the Patent Dance can be avoided. To that end, the two key decisions of 2014 have focused on whether a prospective 351(k) applicant may seek a declaratory judgment of non-infringement.

First, in Celltrion v. Kennedy the prospective biosimilar applicant sought a declaratory judgment against the holder of three method patents covering Remicade®, a treatment for rheumatoid arthritis. The court dismissed the suit on the ground that the biosimilar applicant was too far from receiving FDA approval, and because there was no clear threat of

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12 Id. § 262(1)(3)(A)(i).
13 Id. § 262(l)(6)(B).
14 Id. § 262(l)(8)(A).
15 Id. § 262(l)(8)(B).
16 Id. § 262(9)(A).
17 Id. § 262(9).
18 Id. § 262(l)(1).
infringement.\textsuperscript{21} The court also stated in dicta that it would decline to hear the case in light of the BPCIA, stating that the case was an improper “attempt to skirt the BPCIA’s dispute resolution mechanisms while reaping the benefits of its approval process.”\textsuperscript{22}

Second, in \textit{Sandoz v. Amgen} the prospective biosimilar applicant sought a declaratory judgment against the holder of two composition patents covering Enbrel\textsuperscript{®}, a treatment for autoimmune diseases including psoriasis and rheumatoid arthritis.\textsuperscript{23} The court dismissed the case on two grounds. First, like the court in \textit{Celltrion}, it determined that no case of controversy yet existed between the parties, thus defeating declaratory judgment jurisdiction.\textsuperscript{24} Second, the court held that the suit was barred by the BPCIA, reasoning that, “because Sandoz planned to enter the market by the biosimilarity route, it had to follow the BPCIA’s patent-related procedures applicable to biosimilarity applicants—which it had not done.”\textsuperscript{25} On appeal, the Federal Circuit affirmed on the jurisdictional grounds, and did not address the applicability of the BPCIA.\textsuperscript{26}

Overall, these two decisions have provided little indication on how the BPCIA mechanisms may work in practice, or even under which circumstances they would be triggered. However, another pending case may provide more concrete guidance. As discussed below, that case involves Zarxio\textsuperscript{®}, the first biosimilar licensing application approved in the United States.

\textbf{Zarxio\textsuperscript{®} Licensure and BPCIA Regulatory Outlook}

On March 6, 2015, FDA approved Zarxio\textsuperscript{®} (filgrastim-sndz), the first biosimilar product to be approved in the United States under the BPCIA. Zarxio\textsuperscript{®}’s reference product Neupogen (filgrastim) was approved in 1991 to treat neutropenia, a deficiency of infection-fighting white blood cells caused by cancer and cancer therapies such as bone marrow transplant and chemotherapy. Zarxio\textsuperscript{®} is marketed outside of the United States in more than 60 countries worldwide. Zarxio\textsuperscript{®} was approved in Europe in 2009 as Zarzio, but not in the United States because at the time no regulatory pathway existed to obtain marketing approval for biosimilars. Although the BPCIA was passed in 2010, the process for obtaining approval of a biosimilar under the new law has been long and slow due to a variety of unsettled issues discussed above, including court cases over the BPCIA patent litigation process, and guidances issued by FDA addressing the applicable standards for the approval process.

A significant aspect of the 351(k) approval process addressed in these guidances is that it permits reliance on a variety of types of supporting data, which may or may not include clinical data. On that issue, FDA stated that its “approval of Zarxio\textsuperscript{®} is based on review of evidence that

\textsuperscript{21} Id. at *6-7.
\textsuperscript{22} Id. at *9.
\textsuperscript{24} Id. at *5.
\textsuperscript{25} Id.
\textsuperscript{26} Id. at *8.
included structural and functional characterization, animal study data, human pharmacokinetic
and pharmacodynamics data, clinical immunogenicity data and other clinical safety and
effectiveness data that demonstrates Zarxio is biosimilar to Neupogen.”

Because the issue of biosimilar naming has yet to be settled, FDA designated a
“placeholder nonproprietary name” for Zarxio®, stated that this result “should not be viewed as
reflective of the agency’s decision on a comprehensive naming policy for biosimilar and other
biological products,” and concluded that, “[w]hile the FDA has not yet issued draft guidance on
how current and future biological products marketed in the United States should be named, the
agency intends to do so in the near future.”27 However, as discussed below, the licensure of
Zarxio® still has significant potential hurdles to overcome before launch.

**Zarxio® Case and BPCIA Litigation Outlook**

In October 2014, the reference sponsor filed suit claiming the biosimilar applicant had
not followed the Patent Dance procedures, and seeking declaratory and injunctive relief.28 Unlike
the preceding cases, in *Sandoz v. Amgen II* the biosimilar applicant filed suit against the
reference sponsor after filing and FDA acceptance of its biosimilar application.29

In its complaint, the reference sponsor alleged that instead of providing its application the
biosimilar applicant initially proposed that the parties exchange certain information without
following the process outlined in the BPCIA,30 and then later notified the reference sponsor that
it had decided not to disclose the application and not to exercise its right to use the patent
information exchange process of the BPCIA.31 In addition to common law remedies and patent
infringement, the reference sponsor sought to enjoin marketing of the biosimilar until it was
restored to the position it would have been in had the procedures of the BPCIA been followed.32

In its answer, the biosimilar applicant pointed to BPCIA subsection (l)(9)(C), which
states that if the applicant fails to provide the application under the Patent Dance procedure, the
reference sponsor – not the biosimilar applicant – may bring an action for a declaration of
infringement, validity, or enforceability of the any patent directed to the biologic or its use.33

On the reference sponsor’s motion for preliminary injunction, the biosimilar applicant
argued that under the BPCIA the Patent Dance is not the only path to resolve patent disputes.34
Rather, biosimilar applicants may choose to disclose their application and thereby initiate the

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28 Complaint at 24, Id.
30 Id.
31 Id.
32 Id. at 36-37.
33 Answer at 2, Id. See also Answer at 7-8.
34 Id. at 2.
Patent Dance, or to decline and thus trigger an alternative mechanism explicitly provided in the BPCIA, namely a declaratory judgment action by the reference sponsor.35

On March 19, 2015, court held in favor of the biosimilar applicant, stating that the BPCI is optional despite its use of the term “shall.”36 Specifically, the court found that the Patent Dance “allows an applicant to enjoy a temporary safe harbor from litigation,” but that Congress “expressly directed reference product sponsors to commence patent infringement litigation in the event of an applicant’s non-compliance.”37 The court also held that under the 180 day commercial marketing notice provision FDA approval of the biosimilar is not necessary for the applicant to notify the sponsor of its intent to market.38 Ultimately, the court denied the state law claims,39 allowed the infringement counterclaims to proceed,40 and denied the reference sponsor’s motion for preliminary injunction.41

Because the decision is being appealed, albeit on an expedited basis, it may take well into or beyond 2015 beyond before there is clarity on whether the Patent Dance may be legitimately avoided. The reference sponsor had also filed a Citizen’s Petition requesting FDA to require biosimilar applicants to certify their compliance with the BPCIA procedures, but FDA denied the petition.42

This case is currently unfolding at such a rapid pace that at the time this article goes to press, there will likely have been new developments. If, however, the Sandoz v. Amgen II decision is upheld on appeal, the case may serve as a blueprint for future procedures in which the biosimilar applicant wishes to litigate as soon as possible but without sharing information with the reference sponsor. In that case, the reference product sponsor may have the choice of either attempting to follow the Patent Dance procedure and strike a deal, or to engage in “blind” litigation. Which path the sponsor follows may depend on the perceived strength of its patents.

Conclusion

While FDA’s approval of the first biosimilar is a major step forward in the process of implementing the BPCIA, the regulatory landscape for biosimilars awaits considerable further development and refinement from FDA, leaving significant issues uncertain and open for debate. For example, a number of senators recently noted that “[t]he FDA has not yet issued guidance on some of the key scientific policy questions related to biosimilars, such as naming, labeling,

35 Id. at 10
37 Id. at 10.
38 Id. at 12-14.
39 Id. at 15.
40 Id. at 16
41 Id. at 18.
indication extrapolation, and interchangeability.⁴³ Nevertheless, additional biosimilars applications are following closely on the heels of the Zarxio® approval.