

Biologics, Biosimilars,
Bioequivalents—
Oh My!

By Jessica Benson Cox,
Munjot Sahu, Bridget
Ahmann, and Joe Price

Understanding how these products differ from traditional small-molecule drugs will help product liability litigators prepare to dissect the anticipated FDA regulations and how the regulations may direct future litigation over these products.

Product Liability Considerations for Biologics and Biosimilars

In our 2011 article *We're Not in Kansas Anymore Toto: Product Liability Biologics and Biosimilars*, we discussed the Biologics Price Competition and Innovation Act (BPCIA), legislation passed in 2010 that paved the way

for the introduction of biosimilars in the United States. Bridget Ahmann *et al.*, For The Defense, Aug. 2011, at 41–46, 76. We compared the BPCIA to legislation governing generic pharmaceutical products and analyzed several product liability concerns raised by the legislation. Since that time, the U.S. Food and Drug Administration (FDA) has approved the first biosimilar, Zarxio, for use in the United States. Many unanswered questions remain, however, about how product liability law will act on biosimilars once they actually enter the marketplace. This article explores what makes these products unique, current unanswered questions about how the government will regulate these products, lessons that we have learned from the FDA

approval of Zarxio, and evolving product liability concerns specific to biologics and biosimilars that manufacturers, regulators, and attorneys should all consider.

What Is a Biosimilar?

In general, there are two types of drugs: (1) small-molecule chemical compounds, and (2) large-molecule biologics. Carl J. Minniti III, *Sandoz v. Amgen: Why Current Interpretation of the Biologic Price Competition and Innovation Act of 2009 Is Flawed and Jeopardizes Future Competition*, 97 J. Pat. & Trademark Off. Soc'y 172, 176 (2015). Most drugs available today are small-molecule chemical compounds that are taken orally and typically made by combining specific chemical ingredients in an ordered

■ Jessica Benson Cox is a partner and Munjot Sahu is an associate in the Indianapolis office of Faegre Baker Daniels LLP. Ms. Cox's practice focuses on the defense of pharmaceutical companies and medical device manufacturers in mass torts and class action litigation. Ms. Sahu's practice focuses on drug and medical device litigation, as well as food and agriculture

litigation. Bridget Ahmann and Joe Price are partners in the Minneapolis office of Faegre Baker Daniels LLP. Ms. Ahmann's practice focuses on the defense of manufacturers of pharmaceuticals, medical devices, and dietary supplements in mass tort and class action litigation. Mr. Price's practice focuses on the defense of pharmaceutical and medical device manufacturers in mass tort and class action litigation.



process. Biotechnology Indus. Org., How Do Drugs and Biologics Differ?, <https://www.bio.org/articles/how-do-drugs-and-biologics-differ>. (Nov. 10, 2010, 12:34 PM) (last visited Aug. 5, 2015). These drugs have well-defined chemical structures, and a finished small-molecule drug can usually be analyzed to determine all its various components. *Id.* Biologics, however, are very large, complex molecules, usually proteins, that are derived from living organisms. Whereas a traditional small-molecule drug may contain between a few dozen to a hundred atoms per molecule, the complicated proteins of a biologic can include up to tens of thousands of atoms per molecule, and they are so complex that they can be difficult to characterize with currently used analytical methodologies. Joanna M. Shepherd, *Biologic Drugs, Biosimilars, and Barriers to Entry*, 25 Health Matrix 139, 142 (2015); Martina Weise *et al.*, *Biosimilars: What Clinicians Should Know*, 120 Blood 5111, 5111 (2015). See Figure 1.

Biologics are produced under carefully controlled and monitored conditions, and they are almost always administered by injection or infusion. Examples of biologics include vaccines, insulin, growth hormones, and monoclonal antibodies, which are used to treat many diseases, including cancer. Shepherd, *supra*, at 142; Irish Pharm. Health Care Ass'n, *Balancing Access to Biologics with Patient Safety and Well-Being: An IPHA Position Paper* 8 (2014). Because of the variability inherent in manufacturing living cells, biologics display a certain degree of inconsistency, called *microheterogeneity*, even between different consecutive batches of a biologic from the same manufacturer. Shepherd, *supra*, at 151; Weise *et al.*, *supra*, at 5111.

Biologics are produced by using complex manufacturing processes that take several months from start to finish and that may require twenty times as many separate quality checks compared to small-molecule drugs. Irish Pharm. Health Care Ass'n, *supra*, at 2. In fact, the characteristics and properties of biologics depend so much on the manufacturing process that experts often explain that “the product is the process” for biologics. Biotechnology Indus. Org., *supra* (emphasis added).

Manufacturers of biologics also frequently make changes to their manufac-

turing processes, both during development of a biologic and after approval, to increase scale, improve product stability, and comply with changes in regulatory requirements. Irish Pharm. Health Care Ass'n, *supra*, at 10. These small changes, whether inadvertent or intentional, may alter the final biologic product made by an individual manufacturer and its corresponding safety profile. See Thijs J. Giezen *et al.*, *Safety-Related Regulatory Actions for Biologicals Approved in the United States and the European Union*, 300 JAMA 1887, 1888 (2008) (“Small differences and changes in the production process can therefore have major implications on the safety profile of biologicals.”); Int’l Soc’y for Pharmacoepidemiology, Response to: U.S. Food and Drug Admin. Docket No. FDA-2010-N-0477 Approval Pathway for Biosimilar and Interchangeable Biological Products 2 (2010) (“The vulnerability of biological agents to changes in structure is at the heart of the issues to be considered when planning for safety assessments of these products, since manufacturing, storage and even the mode of administration can alter these structures.”). For example, subtle

changes to manufacturing a biologic may lead to small changes in the final product that increase *immunogenicity*, which occurs when a patient’s immune system develops antibodies to protein-based drugs. Impurities introduced through the manufacturing process pose another risk to biologic products because they can cause immunogenicity reactions. Francesco Locatelli & Harald Becker, *Update on Anemia Management in Nephrology, Including Current Guidelines on the Use of Erythropoiesis-Stimulating Agents and Implications of the Introduction of “Biosimilars*, 14 The Oncologist 16, 19 (2009) (“Impurities derived from the host cell line, from the complex growth media required, and from purification processes themselves are inevitable.”). For example, in 2007–2008, heparin contaminated with over-sulfated chondroitin was linked to hypersensitivity reactions in patients in the United States. Nana Kawasaki *et al.*, *New Era of Glycoscience: Intrinsic and Extrinsic Functions Performed by Glycans*, 32 Biol. Pharm. Bull. 796, 797 (2009). See also *In re Heparin Prods. Liab. Litig.*, 803 F. Supp. 2d 712 (N.D. Ohio 2011).

Figure 1

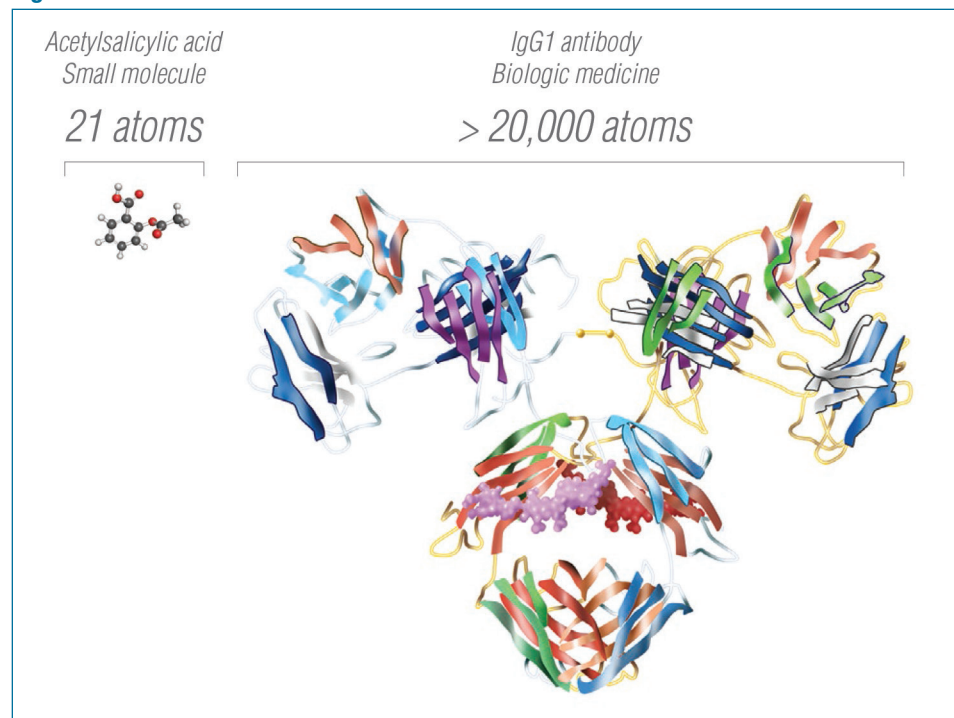


Illustration of a small-molecule drug versus a large, complex biologic. Amgen, Inc., *Biologics and Biosimilars: An Overview* 5 (March 2014), http://www.amgen.com/pdfs/misc/Biologics_and_Biosimilars_Overview.pdf

Immunogenicity and impurities can be specific to one manufacturer or to particular batches of a biologic product. When the manufacturer of Ominotrope, a biosimilar growth hormone, attempted to transfer production between facilities, even though qualitative testing did not show a difference between the end products, a difference in immunogenicity was observed. H. Mellst-

Impurities introduced through the manufacturing process pose another risk to biologic products because they can cause immunogenicity reactions.

edt *et al.*, *The Challenge of Biosimilars*, 19 *Annals of Oncology* 411, 414–15 (2008). With regard to impurities, the same potential for differences among batches manufactured by the same company has been noted. See Barbara Mounho *et al.*, *Global Regulatory Standards for the Approval of Biosimilars*, 65 *Food & Drug L.J.* 819, 828 (2010).

With small-molecule drugs, generic manufacturers are able to make an exact copy of the active pharmaceutical ingredient or ingredients in the branded drug. This effective duplication, or *bioequivalence*, is defined by statute as “the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.” 21 C.F.R. §320.1(e) (effective Jan. 16, 2009). Note, however, that while generic drugs must contain the same active ingredients as brand name drugs, the FDA permits generic companies to use different inactive ingredients. Anna B. Laakmann, Symposium, *The Hatch-Waxman Act’s Side Effects: Precautions for Biosimilars*, 47 *Loy. L.A. L. Rev.* 917, 922 (2014).

While bioequivalence may be established for a chemically synthesized drug with dozens or hundreds of atoms per molecule, “it is impossible to duplicate exactly complex biologics with tens of thousands of atoms per molecule; even a *chemically identical biologic* may produce different effects in the body because of the unique *structural organization pattern* of the proteins (known as *folding*.” Shepherd, *supra*, at 143 (emphasis added). As a result, companies looking to replicate a branded biologic must instead use highly similar, but slightly variant, living organisms or processes in creating a *biosimilar*, a biologic that is highly similar to, but not an exact duplicate of, an existing FDA-approved biologic. Laura Lorenzetti, *FDA Approves the First Biosimilar for the U.S. Market*, *Fortune* (Mar. 6, 2015, 11:53 AM), <http://fortune.com/2015/03/06/fda-approves-first-biosimilar/> (last visited Aug. 5, 2015).

Biosimilars in the United States

The Biologics Price Competition and Innovation Act (BPCIA), signed into law in 2010, established an abbreviated pathway for FDA approval of biosimilar medicinal products, in the hope that increasing the availability of biosimilars would lower the cost of biologic drugs. See 42 U.S.C. §262(k) (effective July 9, 2012). In many ways, the BPCIA is to biologics as the Hatch-Waxman Act is to traditional small-molecule drugs. The BPCIA requires an applicant to demonstrate that the proposed biosimilar is “similar” to the reference product, which means that (1) the applicant’s biologic product is “highly similar” to the reference product; and (2) there are “no clinically meaningful differences” in terms of safety, purity, and potency between the biosimilar and reference product. 42 U.S.C. §262(i)(2).

In addition, an applicant must demonstrate the following:

- The biosimilar will use the same mechanism of action as the reference product for the conditions of use listed in the reference product label;
- The conditions proposed by the biosimilar label have been previously approved for the reference product;
- The biosimilar uses the same route of administration, dosage form, and strength as the reference product; and

- The facility used to manufacture, process, pack, or store the biosimilar meets standards ensuring that the product is safe, pure, and potent. 42 U.S.C. §262(k)(2)(A)(i).

Three types of proof are required to demonstrate safety, purity, and potency: analytical studies showing “high similarity”; animal studies addressing toxicity; and clinical studies assessing immunogenicity, pharmacokinetics, and pharmacodynamics. 42 U.S.C. §262(k)(2)(A)(i)(I).

The BPCIA also allows a biosimilar applicant to seek a determination that it is “interchangeable” with the reference product. 42 U.S.C. §262(k)(2)(B). To achieve classification as an interchangeable, a biosimilar must demonstrate that (1) users can expect it to produce “the same clinical result” as the reference product, and (2) switching between the biosimilar and the reference product will not put patients at risk in terms of safety or efficacy. 42 U.S.C. §262(k)(4). The first biosimilar to be designated as interchangeable with a specific reference product will receive a period of exclusivity of at least one year during which no other biosimilar can attain interchangeable status. 42 U.S.C. §262(k)(6). The BPCIA also outlines that “interchangeable” biosimilars should be allowed to be substituted for the reference product without the intervention of a health-care provider. 42 U.S.C. §262(i)(3). However, in practice, automatic substitution will be governed by state law. See 25 AM. JUR. 2D *Drugs and Controlled Substances* §83 (2015).

In March 2015, the FDA approved the first biosimilar for use in the United States. Zarxio, a biosimilar manufactured by Sandoz, was unanimously recommended for approval by an FDA expert panel. *FDA Approves First Biosimilar Zarxio™ (filgrastim-sndz) from Sandoz*, Novartis (Mar. 6, 2015, 9:10 PM), <https://www.novartis.com/news/media-releases/fda-approves-first-biosimilar-zarxio-™-filgrastim-sndz-sandoz> (last visited Aug. 5, 2015). Zarxio is a biosimilar of Neupogen, manufactured by Amgen, which boosts the production of white blood cells and inhibits infection in patients receiving chemotherapy for certain tumors. Sabrina Tavernise & Andrew Pollack, *F.D.A. Approves Zarxio, Its First Biosimilar Drug*, *N.Y. Times* (Mar. 6, 2015); FDA, *Biosimilars: More Treatment Options Are On the Way*, Consumer Up-

dates (Mar. 6, 2015), <http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm436399.htm> (last visited Aug. 5, 2015). Currently, at least 11 additional biosimilars are in development for use in the United States. Tavernise & Pollack, *supra*. Zarxio's introduction in the United States is expected to save consumers an estimated \$5.7 billion in drug costs over the next 10 years, and consumers could

Even a chemically identical biologic may produce different effects in the body because of the unique structural organization pattern of the proteins (known as *folding*).

save an estimated \$250 billion in drug costs in the same period of time if the biosimilars currently in development are approved by the FDA. *Id.* Zarxio, however, has not been approved as an interchangeable product. Press Release, FDA, *FDA Approves First Biosimilar Product Zarxio* (Mar. 6, 2015), <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm> (last visited Aug. 5, 2015).

In April 2015, the FDA released three guidance documents as part of a series intended to allow the agency to develop its position on the technical development and approval of biosimilar products. FDA Center for Biologics Evaluation and Research, *Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product: Guidance for Industry* (2015) (Quality Considerations Guidance), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf>; FDA Center for Biologics Evaluation and Research, *Scientific Considerations for Demonstrating Biosimilarity to a Reference Product: Guidance for Industry* (2015) (Scientific Considerations Guidance), <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatory>

information/guidances/ucm291128.pdf; FDA Center for Biologics Evaluation and Research, *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009: Guidance for Industry* (2015) (Questions and Answers Guidance), <http://www.fda.gov/downloads/Drugs/Guidances/UCM273001.pdf>. In the quality considerations guidance, the FDA provided additional illumination to the industry on what analytical studies might be relevant to assessing whether a proposed biosimilar and a reference product are "highly similar" to support a demonstration of biosimilarity. FDA, Quality Considerations Guidance, *supra*, at 4. This guidance also describes additional chemistry, manufacturing, and control information that might be relevant to an assessment of whether a proposed product and reference product are highly similar. *Id.*

The scientific considerations guidance provides an overview of the FDA approach to determining biosimilarity, discusses specific scientific considerations in demonstrating biosimilarity, and outlines that the FDA will use a totality-of-the-evidence approach to review applications for biosimilar products, consistent with long-standing agency policy. FDA, Scientific Considerations Guidance, *supra*, at 2. Finally, the questions and answers guidance provides answers to common questions from sponsors about (1) biosimilarity and interchangeability; (2) the FDA's interpretation of the definition of "biologic products" as amended by the BPCIA; and (3) specifics regarding the determination of exclusivity periods for certain products. See generally FDA, Questions and Answers Guidance, *supra*.

While these three guidance documents are helpful in understanding how the FDA will implement certain provisions of the BPCIA, and the specifics surrounding the recent FDA approval of Zarxio may instruct further how the agency may implement the act, many unanswered questions still remain that potentially have a profound effect on product liability and marketing implications for biosimilar products.

What Have We Learned from the Zarxio FDA Approval Process?

Although commentators have widely speculated that the FDA will follow antici-

pated biosimilar naming guidance from the World Health Organization, which administers a global naming convention for drugs, discussing the Zarxio naming experience highlights how these names will affect biosimilar product liability litigation. As for labeling, the Zarxio labeling experience and the debates that it generated over whether or not biosimilars should have product-specific labels demonstrate how labeling also will have far-reaching consequences for future product liability litigation.

How Will Biosimilars Be Named?

Currently, the World Health Organization (WHO) administers a global naming convention for drugs, known as the International Nonproprietary Names (INN) system. The system intends that names facilitate the identification of the active pharmaceutical ingredients in a drug by health-care professionals worldwide. Names under the system are granted based only on the molecular characteristics and pharmacological class of the proposed APIs. Mark McCamish *et al.*, *Biosimilar by Name and Biosimilar by Nature*, The RPM Report 1 (2013). In the United States, a sponsor may obtain a United States Adopted Name (USAN) as the locally assigned INN. Often, the USAN is identical to the INN. *Id.* at 1. For example, both the INN and the USAN (the "generic name") for Amgen's brand-name drug Neupogen is "filgrastim."

Drugs in the United States are also assigned a National Drug Code (NDC) number by the FDA. See 21 C.F.R. §207.25 (effective Mar. 13, 2013); 21 C.F.R. §207.35 (effective Mar. 15, 2011). Each manufacturer's product receives its own NDC, which is often identified in pharmacy distribution and insurance records, but not necessarily in physician prescriptions or health institution patient-care records. A lot number, often located through pharmacy records, can be used to identify the dates on which a product was manufactured and thus further narrow manufacturing identification details. See, e.g., *FDA Public Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products*, Transcript 137 (2010) (testimony of Steven Miller, Express Scripts), <http://www.fda.gov/downloads/Drugs/NewsEvents/UCM289130.pdf> (archival material).

The BPCIA does not specifically address how biosimilars should be named. After its enactment, some manufacturers of innovative biologics opined that due to the potential for variance between a biosimilar and a reference biologic, using unique, nonproprietary names for biologic products would be essential to ensuring patient safety and adequate pharmacovigilance. Krista Hessler Carver *et al.*, *An Unofficial Legislative History of the Biologics Price Competition and Innovation Act of 2009*, 65 Food Drug L.J. 671, 712 n.23 (2010). *See also FDA Public Hearing* at 219 (testimony of Jim Shehan, Novo Nordisk); *J&J Petitions FDA to Require "Similar" Names for Biosimilars*, *Biologics*, 29 Westlaw J. Pharm 9, 9 (2014). Proponents of unique, nonproprietary names for biosimilars argue that most spontaneous reports of adverse events from patients and health-care providers do not include specific product identification information such as NDC numbers, thus giving each biosimilar product a unique product name would increase the odds that an initial report would correctly identify a potentially problematic product and aid in rapid responses to potential safety concerns. These groups argue that this is especially important given the potential for variance between a reference biologic and a corresponding biosimilar. *See Mounho et al.*, *supra*, at 825. *See also Locatelli & Becker*, *supra*, at 19.

In contrast, others have argued that unique names are unnecessary, and the use of a National Drug Code (NDC) and lot numbers would sufficiently identify these products. *See FDA Public Hearing*, *supra*, at 135–36 (2010) (testimony of Steven Miller, Express Scripts) (advocating that “the system of having NDCs actually allows for all the important aspects you need for the safety attribute but still allows for competition in the marketplace so a unique product name for each product is probably not required”). The head of Global Biopharmaceutical Development at Sandoz International and others recently highlighted that it is *the FDA review process*, and not the generic name assigned to a drug, that ensures that a biosimilar product has no “clinically meaningful differences” from a reference biologic in terms of safety, purity, and potency. *McCamish et al.*, *supra*, at 6; 42 U.S.C. §262(i)(2). They explained that

providing unique, nonproprietary names for biosimilars could actually undermine the FDA review process and could lead to confusion in the marketplace that might limit patients’ access to these medications and make assessing safety data more difficult. *See generally McCamish et al.*, *supra*.

In terms of pharmacovigilance, some also argue that using nonproprietary names for biosimilars would not help track adverse events. They point out that nonproprietary names are used in national and regional pharmacovigilance systems to facilitate the detection of new safety information related to pharmaceutical substances on a global level. *McCamish et al.*, *supra*, at 5. Those systems support the aggregation of safety data, detection of class effects, and appropriate and timely responses to safety alerts. *Id.* If biosimilars in the United States have different, nonproprietary names, USANs, they argue, that would “necessarily decouple biosimilars approved in the United States from safety data of the same products elsewhere in the world, where consistent non-proprietary names are currently used, and vice versa.” *Id.*

Zarxio, the first approved biosimilar, has received the “placeholder” nonproprietary name of “filgrastim-sndz”; “filgrastim” is the generic name for Neupogen, and “sndz” stands for Sandoz. Tavernise & Pollack, *supra*. The FDA has made clear, however, that the placeholder name does *not* reflect a comprehensive naming policy for biosimilar and other biological products that the agency will issue in the future. Press Release, FDA, *supra*.

The WHO is expected to release final guidelines on naming biosimilars this year. It is widely speculated that the FDA will follow the forthcoming WHO guidance, but to date, the way in which the FDA will name biosimilars remains uncertain and has significant product liability implications for identifying a product at issue in litigation and the speed with which manufacturers and regulators can respond to potential safety signals. *Ahmann et al.*, *supra*, at 43.

What Is Required in a Biosimilar Product Label?

Under the current regulatory scheme, generic small-molecule drug manufacturers must show that “the labeling proposed for the new drug is the same as the labeling

approved for the [approved brand-name] drug. 21 U.S.C. §355(j)(2)(A)(v) (effective Mar. 13, 2013). Generic manufacturers are also prohibited from making any unilateral changes to a drug’s label after a manufacturer receives approval. *See* 21 C.F.R. §314.94(a)(8)(iii) (effective Mar. 15, 2011); 21 C.F.R. §314.150(b)(10) (West, Westlaw through June 4, 2015). The BPCIA, how-

The BPCIA also outlines
that “interchangeable”
biosimilars should be
allowed to be substituted
for the reference product
without the intervention of
a health-care provider.

ever, does not include this “same label” requirement for biosimilars or outline how the BPCIA will regulate biosimilar product labels.

Given that the potential for adverse reactions with biologics may be specific to a particular manufacturer, or even to a particular batch from a specific manufacturer, some have urged the FDA to allow biologic products to have manufacturer-specific labeling. In the draft version of the scientific considerations guidance, the FDA outlined that a biosimilar product label should disclose that the product is a biosimilar, the scope of its approval, and whether it has been found to be interchangeable. FDA Center for Biologics Evaluation and Research, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product: Draft Guidance for Industry* 21 (Feb. 2012). When this guidance was finalized in April 2015, however, the FDA did not mention biosimilar labeling or the need for a biosimilar product label to provide this information.

Publicly available information from the FDA’s review and approval of Zarxio confirm that Sandoz (the manufacturer of Zarxio) and the FDA came to an agreement

that the label for Zarxio and the reference biologic, Neupogen, “should be essentially the same.” FDA Center for Drug Evaluation and Research, Application Number 125553Orig1s000, Administrative and Correspondence Documents (Correspondence Documents) 211, <http://1.usa.gov/1G6mYf7> (Memorandum of Meeting Minutes) (last accessed Aug. 5, 2015); Correspondence

The FDA has made clear, however, that the placeholder name does *not* reflect a comprehensive naming policy for biosimilar and other biological products that the agency will issue in the future.

Documents, *supra*, at 248 (Preliminary Meeting Comments). These materials also indicate that the FDA provided Sandoz with the label for Neupogen to use “as a template” and instructed Sandoz to track any changes made to this label and provide annotations to explain and to justify any such changes, essentially the same processes required of applicants seeking to market generic small-molecule drugs. See *Letter from Ann T. Farrell, M.D. to John M. Pakulski, R.Ph.*, Correspondence Documents 76; 21 C.F.R. §314.94(a)(8)(iv) (abbreviated new drug applications must contain a “side-by-side comparison” of the proposed generic and reference product labeling that shows “all differences annotated and explained”).

In a recent petition submitted to the FDA, AbbVie Inc. cited specific examples in the approved labeling for Zarxio to illustrate how the concept of labeling a biosimilar in the same way as a reference product may “distort[] the safety and efficacy profile of the biosimilar” by “omit[ting] important safety and efficacy data from studies of the biosimilar while also concealing

the fact that the data that are presented in the labeling were derived from studies of the reference product.” AbbVie Inc., *Citizen Petition to FDA* 15 (June 2, 2015), <http://policymed.typepad.com/files/abbvie---citizen-petition-on-labeling-0615.pdf> (last accessed Aug. 5, 2015).

For example, even though Sandoz conducted clinical trials comparing the frequency of adverse events in patients taking Neupogen to those taking Zarxio, none of this information was included in the approved labeling for Zarxio. Rather, the label includes information on adverse reactions in patients from clinical trials studying Neupogen only, not Zarxio. AbbVie Inc., *Citizen Petition, supra*, at 16 n.93 (citing Sandoz, *Advisory Committee Brief* at 82-90 (Jan. 7, 2015), <http://1.usa.gov/1xBJx6L> (last accessed Aug. 5, 2015)); *Id.* at 16 n.94 (citing Sandoz, Inc., Zarxio Package Insert, Table 2 (Mar. 2015), <http://1.usa.gov/1lp408t> (last accessed Aug. 5, 2015)).

The AbbVie petition also highlights that the label for Neupogen states that antibodies binding to Neupogen were detected in three percent of the patients studied, and the petition warns that the “detection of antibody formation” is difficult and therefore the results for Neupogen should not be compared “to other products.” Amgen Inc., Neupogen Package Insert §6.2 (Mar. 2015), <http://bit.ly/1s2wMyt>. When Zarxio was studied, however, antibodies binding to Zarxio were not observed in any patient. Mark McCamish & Sandoz, Zarxio (filgrastim): Presentation to the Oncologic Drugs Advisory Committee 30 (2015), <http://1.usa.gov/1Pm0tf6> (last accessed Aug. 5, 2015). Yet the Zarxio label includes the same language as the Neupogen label and simply replaces the word “NEUPOGEN” with “filgrastim.” As such, the Zarxio label affirmatively lists that in “clinical studies using filgrastim, the incidence of antibodies binding to filgrastim was 3 percent” and similarly states that these results should not be compared to “other filgrastim products.” Zarxio Package Insert, *supra*, §6.2. It has been argued by some that the potential for inaccuracy arises from the fact that Zarxio was approved with the placeholder USAN of “filgrastim-sndz,” and thus a healthcare provider reading this section of the label may incorrectly conclude that studies reporting the three percent incidence per-

tain only to Zarxio, and not to Neupogen, when in fact the opposite is true. AbbVie Inc., *Citizen Petition, supra*, at 17.

Given the complexity of these products, the fact that biosimilars may have different immunogenicity than the reference product, and the open question of whether or not biosimilars will be allowed to share the same nonproprietary name as the reference biologic, it may be unwise for the FDA to allow manufacturers of biosimilars to use the same labeling as the reference biologic. These debates over whether or not a biosimilar should have product-specific labels also demonstrate that labeling will have far-reaching consequences for future product liability litigation.

The Big Picture for Product Liability Litigation

To date, the product liability implications of biologics and biosimilars rest in uncharted waters. We can, however, assume that the inherent differences between biologics and biosimilar products and traditional small-molecule drug products will have a significant effect on litigation over these products.

Failure to Warn Claims and Preemption

The unanswered questions about how biosimilar products will be labeled have far-reaching implications for future product liability litigation. In general, a drug product may be found to be defective and unreasonably dangerous by virtue of its design, manufacture, the inadequacy of its warnings, or a combination of these. Frank C. Woodside III, *IA-10 Drug Product Liability* §10.05 (67th ed. 2015). Often courts examine a drug’s label to determine whether or not the warnings provided by a drug’s manufacturer were accurate or adequate. See, e.g., *McDowell v. Eli Lilly & Co.*, 58 F. Supp. 3d 391, 403 (S.D.N.Y. 2014) (explaining that in New York, courts must evaluate materials such as the package insert and prescribing information provided by the manufacturer to determine whether the warning was “accurate, clear, consistent on its face, and whether it portrays with sufficient intensity the risk involved in taking the drug”); *Williams v. Ciba-Geigy Corp.*, 686 F. Supp. 573, 579–80 (W.D. La. 1988) (concluding that package insert warnings were “very clear, frank, and comprehensive about the dangers of the drug and ways

of reducing the risk” so that medicine was not “unreasonably dangerous per se”); *Felix v. Hoffmann-LaRoche, Inc.*, 540 So.2d 102, 105 (Fla. 1989) (examining text of package insert and explaining that the adequacy of a prescription drug warning “become[s] a question of law where the warning is accurate, clear, and unambiguous”). If a biosimilar’s label merely recites information about the reference biologic product and does not include specific information pertaining to risks that a manufacturer may be aware of that are specific to the biosimilar product, a court may find the biosimilar’s label fails to provide a warning that is adequate or accurate or both.

How the FDA permits biosimilar manufacturers to label their products will also determine whether or not the manufacturers may assert preemption as a defense in these cases. As noted above, federal regulations *mandate* that generic small-scale drugs contain the same labeling as the brand name reference drug. Given this regulatory scheme, the United States Supreme Court has held that federal law preempts failure-to-warn claims against generic drug manufacturers. *PLIVA, Inc. v. Mensing*, 131 S. Ct. 2567 (2011). The Court reasoned that because FDA regulations require that the generic drug’s label be the same as the brand name drug, a generic manufacturer would violate the federal law if the state tort law imposed different or stronger warnings on the label—making it impossible to comply with both. *Id.* at 2577–78. Because there is no similar provision requiring sameness of labels under the BPCIA or regulations currently, attorneys for biosimilar manufacturers should not expect to assert a preemption defense successfully.

While the Zarxio approval authorized the use of essentially the same label as the reference biologic, it is not clear that this will be mandatory forever for that biosimilar or for other biosimilars in the future. If the FDA permits biosimilar manufacturers to change their labels unilaterally without involving the FDA in response to post-marketing reports, which may or may not be unique to those biosimilars made by those manufacturers, federal law would not preempt state tort law claims. *Compare Mensing*, 131 S. Ct. 2567 (2011), with *Wyeth v. Levine*, 555 U.S. 555, 569–71 (2009) (holding that preemption did not bar claims when there is no ev-

idence that the FDA would prohibit a label change, and it was thus not impossible for drug manufacturer to satisfy both federal regulatory and state tort duties).

Manufacturing Defect Claims

Again, in product cases, plaintiffs may argue that a drug is defective and unreasonably dangerous by virtue of its design, its manufacture, the inadequacy of its warnings, or a combination of these allegations. Woodside, *supra*, §10.05. As one commentator notes, it is relatively uncommon in this day and age to litigate a drug case extensively when the prime contention is that the drug was defectively manufactured:

With the advent of modern products liability law during the mid-1900s, manufacturing defect cases for a variety of reasons began to occupy a decreasing proportion of products liability litigation as the plaintiffs’ bar increasingly challenged the sufficiency of product designs and warnings. This proportional decline in manufacturing defect cases in part reflects improvements in the technology of production engineering, including quality assurance. Moreover, as discussed below, the liability standards governing manufacturing flaw cases are generally quite clear and noncontroversial—there usually is little debate over whether a product containing a physical flaw is “defective.” Thus, manufacturing flaw cases are more likely to settle than design and warning defects cases which by nature involve normative judgments of safety sufficiency.

David G. Owen, *Manufacturing Defects*, 53 S.C. L. Rev. 851, 854 (2002) (citations omitted).

As explained above, small-molecule drugs are made by combining specific chemical ingredients in an ordered process. As discussed above, they are not like biologics—very large, complex molecules derived from living organisms that are completely dependent on lengthy manufacturing processes and are known to change continually over time and result in differences in the safety profile of the product. Given the substantial differences in the length, complexity, and importance of the manufacturing process among biologics and as opposed to small-scale molecule drugs, the allegations

about biologics likely will emphasize defective manufacturing more than currently happens with litigation for their small-molecule drug cousins. Separating design defect from manufacturing defect claims for biologics and biosimilars may also prove to be more challenging given that those in the industry often use the mantra that for biologics, the “process is the product.”

These debates over whether or not a biosimilar should have product-specific labels also demonstrate that labeling will have far-reaching consequences for future product liability litigation.

A rise in manufacturing defect claims also may open biologic manufacturers up to increasing liability in certain jurisdictions. Currently, many states impose a lesser liability on prescription drug manufacturers for defective design than for defective manufacturing. For example, in Utah, prescription drug manufacturers are exempt from strict liability claims based on design defects as a matter of law if the drugs are approved by the FDA, consistent with comment (k) of the Restatement (Second) of Torts §402A regarding unavoidably unsafe products. *Grundberg v. Upjohn Co.*, 813 P.2d 89, 95 (Utah 1991); *Schaerrer v. Stewart’s Plaza Pharm., Inc.*, 79 P.3d 922, 928 (Utah 2003). This exemption, however, applies only to design defect claims; prescription drug manufacturers can still be liable for strict liability claims based on manufacturing defects or inadequate warnings. *Schaerrer*, 79 P.3d at 928.

Design Defect Claims—Reasonable Alternative Design

Not only will manufacturing defect claims likely be prevalent in future litigation

relating to biologics and biosimilars, but changes to the way that plaintiffs are able to prove defective design may also be on the horizon. Currently, many states require that a plaintiff prove the existence of a safer alternative design before finding that a product is defectively designed. *See, e.g., GMC v. Jernigan*, 883 So.2d 646, 662 (Ala. 2003) (stating that to prove a design defect,

Currently, many states impose a lesser liability on prescription drug manufacturers for defective design than for defective manufacturing.

a plaintiff must show that “a safer, practical, alternative design was available to the manufacturer at the time it manufactured the [product]”) (citations omitted); *Matherne v. Poutrait-Morin/Zefal-Cristophe*, 868 So.2d 114, 124 (La. App. 2003) (affirming the district court’s grant of summary judgment when the plaintiff “ha[d] not pointed to a safer, alternative design that would have provided the same benefits”); *Uniroyal Goodrich Tire Co. v. Martinez*, 977 S.W.2d 328, 335 (Tex. 1998) (stating that a plaintiff must show “that the defendant could have provided a safer alternative design” in order to prove a design defect) (citing *Caterpillar, Inc. v. Shears*, 911 S.W.2d 379, 384 (Tex. 1995)).

With traditional small-molecule drugs, the generic version of the branded drug is deemed to be bioequivalent, and generic manufacturers are able to make an exact copy of the active pharmaceutical ingredient in the branded drug. As such, a generic version of a branded drug product is not likely to be used as evidence of a safer alternative design to the branded drug product and vice versa. With biologics, however, biosimilars are “highly similar” to the reference biologic, but they are not exact copies of the reference. *See Shepherd, supra*, at 143 (explaining that while bioequivalence

may be established for a chemically synthesized drug with dozens or hundreds of atoms per molecule, “it is impossible to duplicate exactly complex biologics with tens of thousands of atoms per molecule; even a *chemically* identical biologic may produce different effects in the body because of the unique *structural* organization pattern of the proteins...”).

While the BPCIA mandates that there be “no clinically meaningful differences” in terms of safety, purity, and potency between a biosimilar and its reference product, unavoidable differences between products may not be insignificant. *Compare Carver et al., supra*, at 732 (quoting Woodcock, the director of the FDA Center for Drug Evaluation and Research, as stating “a change in even a single amino acid is not a trivial change whatsoever”), and *Giezen et al., supra*, at 1888 (noting that a small change in production process can “have major implications on the safety profile of biologicals”), with *Glastetter v. Novartis Pharms. Corp.*, 252 F.3d 986, 990 (8th Cir. 2001); *McClain v. Metabolife Intern., Inc.*, 401 F.3d 1233, 1246 (11th Cir. 2005) (“even small differences in chemical structure can sometimes make very large differences in the type of toxic response that is produced”)(internal quotation marks omitted). *See also FDA Public Hearing, supra*, at 170–71 (2010) (testimony of John K. Jenkins, Center for Drug Evaluation and Research Biosimilars Review Committee). In fact, numerous courts have already reasoned that “[e]ven minor deviations in molecular structure can radically change a particular substance’s properties and propensities.” *Glastetter*, 252 F.3d at 990. *See also Rider v. Sandoz Pharm. Corp.*, 295 F.3d 1194, 1201 (11th Cir. 2002). As such, it is conceivable that a reference biologic may be different enough from an approved biosimilar to be used as proof of alternate design\ as well as the reverse.

Conclusion

Biologics and biosimilars are highly complex products, and having a thorough understanding of how these products are different from traditional small-molecule drugs will help prepare product liability litigators for future litigation over these products. Even after the FDA approved the first biosimilar product in the United

States, questions remained about how the FDA will name and label these products. Those unanswered questions paint a cloudy picture, leaving what the future will hold for biosimilar product liability litigation unclear. Carefully drafted FDA guidelines, still forthcoming, which take product liability concerns into consideration, will serve to reduce regulatory ambiguity that could lead to complex and expensive litigation for manufacturers and plaintiffs alike.

The authors thank Emily Kile, a 2015 summer associate in the Indianapolis office of Faegre Baker Daniels LLP, for her assistance in preparing this article. 