Biosimilar Liability

Introduction to Biosimilars and Labeling Issues

By Glenn S. Kerner, Nilda M. Isidro, and Alison Siedor

As biosimilars begin to gain traction in the U.S. pharmaceutical market, the distinct labeling requirements applicable to them are likely to affect product liability litigation in this area, raising implications that are potentially distinct from those applicable to biologics and to small-molecule, generic drugs.

According to the U.S. Food and Drug Administration (FDA), biological products "are the fastest growing class of therapeutic products in the United States," and the global biologics market is expected to reach over $625 million by 2026. U.S. Food & Drug Admin., Industry Information and Guidance, Biosimilars, FDA.gov (July 18, 2018); *Biologics Market to Reach USD 625.6 Million By 2026*, GlobeNewswire (Oct. 10, 2019). As of this writing, twenty-eight biosimilars have been approved by the FDA, but biosimilars have been slow to enter the U.S. market despite these approvals: in the ten years since the first biosimilar was approved, only seventeen of the twenty-eight approved biosimilars have launched. Zachary Brennan, *U.S. Biosimilar Launches About to Turn a Corner*, Regulatory Affairs Professionals Society (Mar. 16, 2020); Tony Hagen, *Merck Follows Rivals With US Launch of Trastuzumab Biosimilar* (April 15, 2020); (FDA, *Biosimilar Product Information: FDA-Approved Biosimilar Products* (accessed August 12, 2020), https://www.fda.gov/drugs/biosimilars/biosimilar-product-information). However, biosimilar launches seem to be gaining speed: nine of the seventeen biosimilar launches have occurred since November 2019. *Approval and launch dates for US biosimilars*, Generics and Biosimilars Initiative (June 19, 2020), http://www.gabionline.net/Reports/Approval-and-launch-dates-for-US-biosimilars. As these products enter

■ Glenn S. Kerner is head of the litigation department in Goodwin Procter LLP's New York City office, and chair of the firm's product litigation and counseling practice. He has extensive experience in product liability law, particularly with respect to complex mass torts and multidistrict litigation. Mr. Kerner is experienced in matters involving pharmaceuticals and medical devices, cannabis, food and dietary supplements, consumer products, emerging technologies and chemical exposure. He also has experience in complex commercial litigation, franchise law, bankruptcy litigation, real estate litigation, antitrust, intellectual property, and other civil litigation Nilda M. Isidro is a partner in Goodwin's product litigation and counseling practice, food and healthy living practice, and cannabis practice in the firm's New York City office. She focuses her litigation practice on consumer product law, including mass torts, and multidistrict litigation. Ms. Isidro also provides strategic counseling to a variety of businesses on issues including regulatory compliance, product warranties, risk management, and litigation avoidance. Alison Siedor is an associate in Goodwin's New York City office. She focuses her practice on representing clients in intellectual property litigation, as well as pharmaceutical and medical device manufacturers in product liability actions.

the market and begin to be used more frequently, there is an increased likelihood that they may become the targets of product liability litigation. Although in many ways biosimilars are analogous to small-molecule generic pharmaceutical products, regulatory differences could have important implications for the viability of certain product liability claims that could be asserted for biosimilar products, including claims grounded in failure-to-warn.

In this article, we will provide an overview of biosimilar regulations—particularly the difference between biosimilar-labeling requirements and small-molecule, generic-drug labeling requirements—and assess how these differences will likely affect future product liability litigation involving biosimilars.

Introduction to Biologics and Biosimilars

A biologic product is one developed from, or containing components of, living organisms. Ctr. for Biologics Eval. & Res., *What Are "Biologics" Questions and Answers*, FDA.gov (Feb. 6, 2018). Insulin was the first biologic to be marketed, in 1982. Cong. Res. Srvc., *Biologics and Biosimilars: Background and Key Issues* 6 (June 6, 2019). Today, hundreds have been approved. Biologics are generally highly complex, large-molecule drugs, and they include categories such as therapeutic proteins and monoclonal antibodies. *Id.* at 24. Monoclonal antibodies are immunoglobulin molecules designed to function as substitute antibodies, targeting certain cells and functioning with other parts of the immune system to destroy the targeted cells. Am. Cancer Soc'y, *Monoclonal Antibodies and Their Side Effects*, Cancer.org (Dec. 27, 2019).

Biologics are much larger than small-molecule drugs. For example, the small-molecule drug aspirin contains nine carbon atoms, eight hydrogen atoms, and four oxygen atoms, while the biologic Remicade contains over 6,000 carbon atoms, almost 10,000 hydrogen atoms, and about 2,000 oxygen atoms. Cong. Res. Srvc., *supra*, at 1. Because of their size and manufacturing complexity, biologics are on average covered by more patents than small-molecule drugs. Muthukrisnakumar Kandasamy et al., *Maintaining Patents Protecting Biologics or Small-Molecule Drugs*, 30 Nature Biotech. 50, 53 (2012). This extensive patent protection has been one reason for the delay in market entrance for biosimilars.

For a biologic to be licensed for marketing, the applicant must submit a Biologic License Application (BLA) to the FDA, demonstrating that the biological product, and the facility in which it is manufactured, meet standards to assure that the product is safe, pure, and potent. Cong. Res. Srvc., *supra*, at 4. Biosimilars are large-molecule biological products that have been demonstrated, through an abbreviated Biologics License Application (aBLA), to be "highly similar" to an FDA-licensed biologic. *Id.* at 5. (In the biosimilar context, biologics are also called the "reference product.") Reference products and biosimilars receive nonproprietary names according to an FDA system. In this naming system, each biosimilar or reference product receives a "proper" name; the proper name consists of a "core" name and a four-letter suffix. U.S. Food & Drug Admin., Guidance for Industry: Nonproprietary Naming of Biological Products (Update) (Mar. 2019). The core name is shared by both the reference product and any licensed biosimilar products, but each different product will contain a different four-letter suffix. *Id.* The FDA maintains an online reference called the Purple Book, which lists details for each approved biologic and biosimilar, including BLA and aBLA approval dates, dosage and administration information, proper and proprietary names, and product labels and medication guides. *See* U.S. Food & Drug Admin., Purple Book: Database of Licensed Biological Products.

Although not an exact comparison, it can be helpful to think of biologics as similar to small-molecule, branded drugs, and biosimilars as similar to small-molecule, generic drugs. Analogous to how small-molecule, branded drug applicants must submit a New Drug Application (NDA) to the FDA, biologic applicants must submit a BLA. And just as small-molecule, generic drug applicants can piggyback on an already approved NDA and submit an Abbreviated New Drug Application (ANDA) for faster approval, so too can biosimilars submit an aBLA and demonstrate similarity to the reference product. However, because of the size and complexity of biologics and biosimilars, the regulatory framework surrounding biosimilar approval and labeling differs somewhat from that covering small-molecule, generic drugs. These differences may have implications for future product liability cases brought against biosimilars.

Biosimilar Regulatory Framework

The Biologics Price Competition and Innovation Act of 2009 (the BPCIA) created an abbreviated licensure pathway for biosimilars. Although the core policy goal behind the BPCIA is similar to that of the Hatch-Waxman Act for small-molecule, generic drugs, there are key differences. First, the process for patent litigation is much different for biologics and biosimilars than for small-molecule drugs. The BPCIA provides BLAs with a twelve-year period of exclusivity, as opposed to the five years of exclusivity granted for small-molecule branded drugs, and aBLA applicants must undergo a complex series of disclosures and negotiations during the patent litigation process, called the "patent dance." Guide to Biosimilars Litigation and Regulation in the U.S., §2:1, BPCIA litigation generally (Oct. 2019). Along with the large number of patents covering biologics that are asserted against biosimilar manufacturers, this has been one reason for the delay in biosimilars entering the market. *Id.*

Second, demonstrating similarity to a reference product is different for biosimilars under the BPCIA than it is for small-molecule ANDA filers. An aBLA applicant may rely on the safety and effectiveness data of the reference product. *Id.* The aBLA applicant must demonstrate only biosimilarity, not bioequivalence. Cong. Res. Srvc., *supra*, at 5–6. This is because biosimilars are much more complex than small-molecule drugs, and so it would be nearly impossible for a biosimilar to demonstrate bioequivalence. *Id.* Biosimilarity is defined as being "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and having "no clinically meaningful differences [from] the reference product in terms of… safety, purity, and potency." 42 U.S.C.A. §262(i)(2). Bioequivalence, on the other hand, is defined 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…." 21 C.F.R. §314.3.

To demonstrate biosimiliarity, an aBLA must contain the following elements:

- analytical studies showing that the biosimilar is highly similar to the reference product, notwithstanding minor differences in clinically inactive components;
- animal studies (including an assessment of toxicity); and
- a clinical study or studies (including an assessment of immunogenicity and pharmacokinetics or pharmacodynamics) that are sufficient to demonstrate the safety, purity, and potency of the biosimilar in one or more appropriate conditions of use for which the reference product is licensed.

42 U.S.C.A. §262(k)(2)(A)(i)(I)(aa)–(cc).

The BPCIA also allows a biosimilar applicant to earn "interchangeability" status with a reference product. This requires an additional showing, beyond evidence demonstrating biosimiliarity in the aBLA, that the biosimilar "can be expected to produce the same clinical result as the reference product in any given patient." 42 U.S.C.A. §§262(k)(4)(A)(i)–(ii). Once a biosimilar receives an interchangeable designation, it "may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product." 42 U.S.C.A. §262(i)(3). As of this date, no biosimilar has yet achieved an interchangeable designation. Ctr. for Drug Eval. & Res., *List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations*, FDA.gov (Mar. 2020). *See also* Purple Book, *supra*. But nearly all states have implemented legislation allowing a pharmacist to substitute an interchangeable biosimilar for a prescribed biologic reference product. *See, e.g.*, Ala. Code §34-23-8.1 (West 2020); Cal. Bus. & Prof. Code §4073.5 (West 2020); Fla. Stat. Ann. §465.0252 (West 2020); Ga. Comp. R. & Regs. 480-51-02 (West 2020); Haw. Rev. Stat. Ann. §328-92 (West 2019); Idaho Admin. Code r. 27.01.01.404 (West 2019); 201 Ky. Admin. Regs. 2:116 (West 2020); Mass. Gen. Laws Ann. ch. 112, §12EE (West 2020); Miss. Code. Ann. §73-21-117 (West 2020); N.D. Cent. Code Ann. §19-02.1-14.3 (West 2020); N.H. Rev. Stat. Ann. §318:47-dd (West 2020); N.J. Admin. Code §13:39-7.23 (West 2020); Or. Admin. R. 855-041-1105 (West 2020); 22 Tex. Admin. Code §309.3 (West 2020); Va. Code Ann. §54.1-3408.04 (West 2019).

Biosimilar Labeling

Because of the differences between a reference product and an approved biosimilar, the labeling for a biosimilar may differ somewhat from a reference product's label. The FDA's July 2018 final labeling guidance (Biosimilar Labeling Guidance) states that biosimilar product labeling should incorporate relevant data and information from the reference product labeling, but it otherwise does not require that the biosimilar label be identical to the reference product's label. U.S. Food & Drug Admin., Labeling for Biosimilar Products: Guidance for Industry 5 (July 2018) ("Certain differences between the biosimilar and reference product labeling may be appropriate.… [B]iosimilar product labeling may include information specific to the biosimilar product that is necessary to inform safe and effective use of the product, including administration, preparation, storage, or safety information."). For example, the Biosimilar Labeling Guidance explains that a biosimilar label may include "information *specific to the biosimilar product* that is necessary to inform safe and effective use of the [biosimilar] product." *Id.* (emphasis added). A biosimilar label may also differ from the reference product label if the biosimilar product is seeking licensure for "fewer than all conditions of use of the reference product." *Id.* And even sections of the biosimilar product labeling that are based on the reference product labeling "need not be identical to the reference product labeling," although the Biosimilar Labeling Guidance states that they should be similar to the reference product label's corresponding sections. *Id.*

For biosimilar label warnings and precautions, the Biosimilar Labeling Guidance recommends that the label specify whether the risk or safety information applies to both the biosimilar and reference product, or to just the biosimilar product. *Id.* If the risk or safety information applies to both the biosimilar and the reference product, the biosimilar label should indicate so by using the core name of the reference product. If the risk or safety information is applicable only to the biosimilar, then the label should indicate this by using the biosimilar's proper name (the core name, followed by the approved, four-letter suffix), or by using the biosimilar's proprietary name. *Id.* at 5–7. For example, if an adalimumab biosimilar manufacturer wanted to warn of a risk that applied to all adalimumab products (both the reference product and the biosimilar product), it should include a warning on the biosimilar label that certain adverse events were associated with "adalimumab products." *Id.* at 6–7. If the manufacturer needed to warn of a risk that applied only to the biosimilar itself, the label should specify that certain adverse events were associated with "[biosimilar's proprietary name]" or, if a proprietary name is not available, "adalimumab-[xxxx]." *Id.*

Biosimilarity is defined as being "highly similar to the reference product notwithstanding minor differences in clinically inactive components" and having "no clinically meaningful differences [from] the reference product in terms of… safety, purity, and potency."

A biosimilar applicant must take steps to change the content of its product labeling when it becomes aware of new information that renders the label inaccurate, false, or misleading. But it cannot do so unilaterally: under 21 C.F.R. 601.12, a biosimilar manufacturer must submit to the FDA a supplement for any labeling changes required in

21 C.F.R. 201.57(a) (such as dosage forms and strengths, route of administration, indications and usage, contraindications, warnings and precautions, and adverse reactions). *See* 21 C.F.R. 601.12(f); 201.57(a). However, in some instances, a biosimilar manufacturer can distribute the drug with the updated labeling *before* FDA approval of the updated labeling. 21 C.F.R. 601.12(f)(1)–(2). This circumstance applies only if the labeling changes were based on "newly acquired" information that was not previously submitted to the FDA (such as new clinical studies or new adverse event reports), or if the information was based on new analyses of previously submitted data, and only if the labeling changes were made for one or more of these purposes:

- add or strengthen a contraindication, warning, precaution, or adverse reaction for which the evidence of a causal association satisfies the standard for inclusion in the labeling;
- add or strengthen a statement about abuse, dependence, psychological effect, or overdosage;
- add or strengthen an instruction about dosage and administration that is intended to increase the safety of the use of the product; or
- delete false, misleading, or unsupported indications for use or claims for effectiveness.

21 C.F.R. 601.12(f)(2).

Courts may not apply the same impossibility-preemption principles to biosimilar failure-to-warn claims, because, as explained above, FDA guidelines permit a biosimilar's label to differ from the reference product's label in certain circumstances.

Labeling and Failure-to-Warn Litigation

With small-molecule generics, federal law preempts failure-to-warn claims brought under state law because federal law requires that the generic product label be "the same as the labeling approved for the [brand-name] drug[.]" *See* 21 U.S.C.A. §355(j)(2)(A)(v); *PLIVA, Inc. v. Mensing*, 564 U.S. 604 (2011).

Impossibility Preemption

In *Mensing*, the Supreme Court reasoned that because the FDA asserted that the generic manufacturers could not unilaterally amend a warning label, it would have been impossible for the generic manufacturers to fulfill state tort-law requirements without violating the federal requirement that the generic label be the same as the brand-name label. *PLIVA*, 564 U.S. at 616–19. Thus, impossibility-preemption applied. *Id.*

The *Mensing* Court held that even if the generic manufacturers had requested that the FDA allow them to strengthen their label warnings, it would not have changed the impossibility-preemption analysis: "[t]he question for 'impossibility' is whether the private party could *independently* do under federal law what state law requires of it"; because federal law required that a generic product label match the brand-name counterpart, a generic manufacturer could not, under federal law, independently strengthen its own generic product label. *Id.* at 619–20 (emphasis added).

Courts may not apply the same impossibility-preemption principles to biosimilar failure-to-warn claims, because, as explained above, FDA guidelines permit a biosimilar's label to differ from the reference product's label in certain circumstances. If the FDA permits biosimilar manufacturers to change their labels unilaterally when additional safety information is discovered, without involving the FDA, then a plaintiff may try to argue that the biosimilar manufacturer would be able to include additional warnings on the biosimilar label without running afoul of either federal requirements or state tort law. For example, if a biosimilar product is discovered to cause an adverse reaction that is not shared by the reference product, a court could determine that a biosimilar label that merely copies the reference product's label and does not include information about the biosimilar-specific additional risks failed to provide an adequate warning, because under 21 C.F.R. 601.12, the biosimilar may be distributed with the updated labeling before the labeling change is approved by the FDA. On the other hand, if the FDA ever required a certain biosimilar to use the same label as the reference product, impossibility preemption could apply to that biosimilar.

Field Preemption and Primary Jurisdiction

In addition to impossibility preemption, it is possible that field preemption or primary jurisdiction could be applied to block state-law product liability claims against biosimilars.

Field preemption occurs when states attempt to regulate a field where a pervasive scheme of federal regulation already exists. *Com. of Pa. v. Nelson*, 350 U.S. 497, 502-04, 76 S. Ct. 477, 100 L. Ed. 640 (1956) (holding that if "the scheme of federal regulation [is] so pervasive as to make reasonable the inference that Congress left no room for the States to supplement it," state law is preempted "regardless of whether it purports to supplement the federal law"). For example, courts might find that Congress did not intend for the states to interfere with the pervasive federal regulatory scheme pertaining to biosimilars under the BPCIA, and so they might hold that field preemption bars any state-law product liability claims against biosimilars. *See Amgen Inc. v. Sandoz Inc.*, 877 F.3d 1315, 1327–30 (Fed. Cir. 2017) (holding that the BPCIA preempts state-law unfair competition claims brought against biosimilar applicants for failing to follow provisions of the BPCIA because the BPCIA's comprehensive framework demonstrates congressional intent that federal law exclusively occupy the field, and noting that "[s]imilarly, the FDA has exclusive authority to license biosimilars pursuant to the provisions [of the BPCIA].").

Courts could also apply the primary-jurisdiction doctrine, which "is concerned with 'promoting proper relationships between the courts and administrative agencies charged with particular regulatory duties.'" *Ellis v. Tribune Television Co.*, 443 F.3d 71, 81 (2d Cir. 2006) (quoting *U.S. v. Western Pac. R. Co.*, 352 U.S. 59, 63, 77 S. Ct. 161, 1 L. Ed. 2d 126, 16 Pub. Util. Rep. 3d (PUR) 265 (1956)). Factors involved in applying the primary-jurisdiction doctrine include (1) whether the question at issue is within the conventional experience of judges, or whether it involves technical or policy considerations within the agency's particular field of expertise; (2) whether the question at issue is particularly within the agency's discretion; (3) whether there exists a substantial danger of inconsistent rulings; and (4) whether a prior application to the agency has been made. *Id.* at 82–83. If a court determined that these factors were met, and the issues involved in a state-law tort proceeding against a biosimilar manufacturer were within a federal agency's field of expertise, a court might decide to stay the proceedings and defer the issues to the federal agency.

Protecting a Biosimilar Through Labeling

Because biosimilar manufacturers cannot be certain that preemption will apply to product liability claims brought against biosimilars, they should not rely exclusively on the reference product's labeling. Rather, they should conduct their own assessment of the adequacy of the warnings and instructions contained in the reference product's labeling, and then they should determine whether any additional information, or any stronger warnings, are warranted under 21 C.F.R. 601.12(f). These changes, if any, should be submitted to the FDA as soon as possible.

However, if the labeling changes are within those enumerated in 21 C.F.R. 601.12(f)(2) (e.g., contraindications, warnings, precautions, or adverse reactions; information regarding abuse, dependence, psychological effect, or overdosage; instructions about dosage and administration; or deleting false, misleading, or unsupported indications for use or claims for effectiveness), then those changes should be made to the label immediately. *See* Biosimilar Labeling Guidance, *supra*, at §III.

Because biosimilar failure-to-warn claims are an untested area of law, biosimilar manufacturers should keep close watch on any legal or regulatory developments, including any future FDA guidance, involving biosimilar labeling. FD