Beware Biosimilars

Complex Product Liability Questions for Complex Large-Molecule Biologics

By Carole W. Nimaroff and Jonathan N. Misk

Even with a complete regulatory framework for biosimilar products—both standard and interchangeable—the existing FDA guidance and comparable decisional law for other products offers some ideas about mitigating litigation risks.

On March 6, 2015, the U.S. Food and Drug Administration (FDA) licensed Sandoz's Zarxio under section 351(k) of the Biologics Price Competition and Innovation Act (BPCIA), marking the first time that a biosimilar was approved for marketing in the United States. Just over one year later, on April 5, 2016, the FDA similarly licensed Celltrion's Inflectra. Two additional biosimilars—manufactured by Amgen and Sandoz Inc.—are under active FDA consideration, having received the approval of relevant FDA advisory committees. These landmark approvals have set in motion what is likely to be a cascade of licensures of biosimilars by the FDA; indeed, manufacturers have to date proposed over 50 biosimilar products that are awaiting final approval.

But despite the excitement surrounding this new class of drug, which is expected to offer patients additional and more affordable treatment options, many important questions remain. For in-house lawyers and outside counsel, the most significant of those questions involves identifying the various product-based claims that manufacturers of biosimilars may face—and assessing the likelihood of a plaintiff's success on those claims. This task, however, is daunting, with few analogous products already in the marketplace to which counsel may compare biosimilars. Similarly, while the European Medical Association (EMA) implemented a framework for biosimilar regulation more than a decade ago and approved the first biosimilar in 2006, it does not appear that biosimilar manufac-

■ Carole W. Nimaroff is a counsel and Jonathan N. Misk is an associate in the New York City office of Hughes Hubbard & Reed LLP, practicing in the firm's Product Liability and Toxic Torts Practice Group. Ms. Nimaroff has represented a broad spectrum of pharmaceutical and medical device manufacturers in mass tort product liability litigations in both multidistrict and state coordinated proceedings. She is licensed to practice in New York, New Jersey, and Florida, and maintains memberships in the DRI Drug and Medical Device Committee and the ABA Product Liability Committee. Mr. Misk's practice similarly focuses on the defense of major product liability actions in both federal and state court, and he has extensive experience successfully handling complex legal issues and appellate preservation at the trial court level. He is licensed to practice in New York and Florida.

turers have yet faced any product liability litigation specific to the drugs in Europe. Accordingly, before assessing the merits of product liability claims against biosimilar manufacturers, litigators need to consider the critical differences between biosimilars and other drugs already in the marketplace, especially generics, mine the existing case law regarding those drugs as one source of guidance, and be extremely creative in analyzing the existing regulatory framework for biosimilars.

A number of skilled practitioners have offered high-level analyses of the regulations surrounding biosimilars (or lack thereof) and have recognized possible product liability claims that biosimilar manufacturers may face. *See, e.g.*, Desiree Ralls-Morrison, *Biosimilars—The Emerging Landscape for Pharmaceutical Companies*, Am. Conf. Inst. Drug & Med. Device, May 2016. Building on the solid foundation that those analyses have laid, and acknowledging the ever-changing world of product liability litigation, this article explores in greater depth—and with reference to previous claims levied against pharmaceutical companies—a selection of some interesting product liability issues surrounding biosimilars. More specifically, the remainder of this article assesses the FDA's various draft guidance on biosimilars and a number of manufacturers' comments on the subject and addresses (1) the viability of design-defect claims—which are currently disfavored in the pharmaceutical context—against biosimilar manufacturers; (2) the viability of failure-to-warn claims against biosimilar manufacturers and the availability to them of the preemption and lack of proximate causation defenses, which are established defenses available to generics manufacturers; (3) the potential increase of manufacturing defect claims against biosimilar manufacturers, which are rarely seen with traditional drugs; and (4) the potential for false advertising and marketing claims, particularly against non-interchangeable biosimilar manufacturers that may choose to market their products actively.

What Are Biosimilars Anyway? A Brief Primer on Key Terminology

Understanding the product liability landscape surrounding biosimilars requires having at least a basic understanding of what biosimilars are. The advent of biosimilars can be traced to the passage of the Patient Protection and Affordable Care Act (ACA), which "create[d] an abbreviated licensure pathway… for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product. FDA, *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, Guidance* 1 (2015) (*Scientific Considerations*), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Simply stated, a biosimilar is a biological medical product that has a certain level of similarity to another already approved biological product.

Stepping back for a moment, a "*biological product*" or "*biologic*" is a drug approved by the FDA for treatment of specific conditions, but the structure of biologics is far more complex than that of traditional drugs, which consist of pure chemical substances and are manufactured with specific chemical "recipes." A biologic is a large-molecule, "complex mixture[] that [is] not easily identified or characterized." *See FDA 101: Regulating Biological Products*, FDA (Nov. 18, 2015) (*FDA 101*), http://www.fda.gov/. Biological products are "made from a variety of natural resources—human, animal, and microorganism—,"and they "replicate natural substances such as enzymes, antibodies, or hormones." *Id.* They "can be composed of sugars, proteins, or nucleic acids, or a combination of these substances," and they can even be "living entities" such as "cells and tissues." *Id.* Because biologics have *no* readily identifiable chemical blueprint, they are not easily produced.

A "*biosimilar*" is a biologic that "is highly similar" to an already approved biological product, meaning that "there are no clinically meaningful differences between the products in terms of safety, purity, and potency." *Scientific Considerations*, *supra*, at 8. It is important to note that a biosimilar is *not* an exact copy of the "already approved product[]," known as the "*reference product*." *FDA 101*, *supra*. The FDA permits "minor differences in clinically inactive components" in biosimilars. *Scientific Considerations*, *supra*, at 4. In short, a biosimilar may work the same way as the reference product, but it is not a copy of it; for the sake of comparison to generics, the "dissimilarity" is among the most significant differences that will likely affect the way that the biosimilars are treated in product liability litigation.

An "*interchangeable*" is a biosimilar that "meets additional standards" and the FDA allows substitution of the interchangeable for the reference product without any additional action or "intervention of the health care provider who prescribed the reference product." *Information on Biosimilars,* FDA (May 10, 2016), http://www.fda.gov/. These "additional standards" for interchangeability include, but are not limited to, (1) "information to show that the proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient"; and (2) "for a biological product that is administered more than once to an individual[,]… information to demonstrate that the risk in terms of safety or diminished efficacy of alternating or switching between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternating or switching." *Information for Industry (Biosimilars)*, FDA (May 10, 2016) (*Information for Industry*), http://www.fda.gov/. The goal of this additional approval status is to establish a certain level of biosimilarity "'between the proposed product and a reference product, not to independently establish the safety and effectiveness of the proposed product.'" *See* John T. Aquino, *FDA Stays Mum on Interchangeable Biosimilar Guidance*, Bloomberg BNA (Apr. 13, 2016), http://www.bna.com/ (requires subscription) (citation omitted). As discussed below, this common feature of "substitutionability" shared by interchangeables and

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generic drugs could have legal implications that counsel should consider.

Night of the Living Design-Defect Claim?

Design-defect claims against pharmaceutical manufacturers are generally disfavored. Many jurisdictions—especially those that have adopted comment k to section 402A of the Restatement (Second) of Torts—will not even recognize strict liability design-defect claims against prescription drug manufacturers because the products are highly beneficial despite carrying known risks. *See* Restatement (Second) Torts §402A cmt. k (Am. Law Inst. 1975) ("There are some products which… are quite incapable of being made safe for their intended and ordinary use.… The seller of such products… with the qualification that they are properly prepared and marketed, and proper warning is given… is not to be held to strict liability… merely because he has undertaken to supply the public with an apparently useful and desirable product, attended with a known but apparently reasonable risk.").

The growing prevalence of biosimilars is certain to bring additional questions concerning at least negligent design-defect claims.

Negligent design-defect claims against pharmaceutical manufacturers are also rarely successful because most jurisdictions require plaintiffs to demonstrate the existence of a reasonable alternative design to prevail with such a claim. *See, e.g.*, *Tersigni v. Wyeth*, 817 F.3d 364, 368 (1st Cir. Mar. 23, 2016). As the First Circuit recently explained, demonstrating the existence of a reasonable alternative design "requires the plaintiff to show that the product in question could have been more safely designed, not that a different product was somehow safer." *Id.* But meeting such a high burden is often difficult "because altering the design often alters the nature and efficacy of the product," thus effectively meaning that the altered design is not a reasonable alternative at all. *See* Ralls-Morrison, *supra*, at 14.

The growing prevalence of biosimilars is certain to bring additional questions concerning at least negligent design-defect claims. While it seems unlikely that strict liability design-defect claims will suddenly gain traction since as with any other biological product or pharmaceutical, biosimilars are "apparently useful and desirable product[s], attended with a known but apparently reasonable risk," defense counsel must consider whether the very qualities that define biosimilars could actually aid in the success of negligent design-claims involving either biosimilars or their reference products.

On the one hand, since a biosimilar is, by definition, a product only "*highly similar*"—rather than identical—to its reference product, plaintiffs could conceivably point to either the biosimilar or the reference product as evidence of a "reasonable alternative design" should any actionable issues arise with the other product. *See* Ralls-Morrison, *supra*, at 14. *See also* Jessica Benson Cox *et al.*, *Biologics, Biosimilars, Bioequivalents—Oh My!, Product Liability Considerations for Biologics and Biosimilars*, For The Defense, Sept. 2015, at 31–32. On the other hand, however, because a biosimilar cannot have any "clinically meaningful differences" from its reference product, as codified in 42 U.S.C. §262(i)(2) (2012), it remains to be seen whether courts would conclude that such a product could legally constitute a "reasonable alternative design" for the purposes of a negligent design-defect claim.

Even if a plaintiff satisfies the fundamental prerequisites of each element of a negligent design-defect claim against a biosimilar manufacturer, the claim may still be preempted. Although the FDA has made clear that biosimilars and generics are not the same, counsel should examine decisional law regarding generics to assess how these differences may affect a court's treatment of negligent design-defect claims against biosimilar manufacturers. The Supreme Court's decision in *Mutual Pharmaceutical Co., Inc. v. Bartlett*, 133 S. Ct. 2466 (2013), is particularly instructive. In *Bartlett*, the Supreme Court focused on the factual "impossibility of redesigning" the generic drug in question; as the Court explained, "redesign was not possible" in part because "the FDCA requires a generic drug to have the same active ingredients, route of administration, dosage form, strength, and labeling as the brand-name drug on which it is based." *Id.* at 2475. Accordingly, the manufacturer "'[could not] legally make [the generic drug] in another composition'" because, were it "to change the composition of [the generic drug], the altered chemical would be a new drug that would require its own NDA to be marketing in interstate commerce." *Id.* (citation omitted). Similar reasoning may apply to biosimilars; indeed, FDA regulations dictate that biosimilars have "no clinically meaningful differences… in terms of safety, purity, and potency" from their reference product, allowing only minor differences in clinically inactive components. *Scientific Considerations*, *supra*, at 8. In other words, biosimilars must have the same active ingredients and work in the same way as the reference product upon which it is based. *Cf. Bartlett*, 133 S. Ct. at 2475. Defense counsel thus retain a colorable argument that federal law preempts state law design-defect claims against biosimilar manufacturers. *Id.* Ultimately, however, the availability of such a preemption defense to biosimilar manufacturers will boil down to whether courts decide that the "highly similar" and "no clinically meaningful differences" requirements for biosimilars are sufficiently comparable to the "same as" requirement for generics.

Further to this point, it would seem that interchangeable biosimilars might enjoy a stronger preemption defense against negligent design-defect claims than standard biosimilars because, as explained more fully below, the FDA recognizes that interchangeables are more similar to generic pharmaceuticals than standard biosimilars are since pharmacists may freely swap interchangeables and their reference products, just as generics and brand-name drugs are readily substituted. *See, e.g.*, FDA, *Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009: Draft Guidance* 4

(May 12, 2015), http://www.fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/Guidances/UCM273001.pdf. ("Interchangeable products may be substituted for the reference product without the intervention of the prescribing healthcare provider." (citation omitted)); *Information for Industry*, *supra* ("For a product to be reviewed as an interchangeable product, manufacturers must include information demonstrating biosimilarity, and include information to show that the proposed interchangeable product is expected to produce the same clinical result as the reference product in any given patient."). *See also Bartlett*, 133 S. Ct. at 2473; *PLIVA, Inc. v. Mensing*, 564 U.S. 604, 618–19 (2011). This fundamental distinction of substitution by pharmacists may strengthen a biosimilar manufacturer's preemption defense to negligent design-defect claims as applied to interchangeable biosimilar products versus standard biosimilar products.

Failure-to-Warn and Other Misleading Labeling Claims

Failure-to-warn claims, similar to design-defect claims, are among the causes of action that plaintiffs typically allege in virtually every product liability lawsuit. Failure-to warn-claims require plaintiffs to demonstrate that a manufacturer has failed to (1) warn about a product's risks, of which it knew or should have known; or (2) provide adequate instructions concerning proper handling of the product. *See, e.g.*, Restatement (Third) of Torts: Prod. Liab. §2(c) (Am. Law. Inst. 1998). Plaintiffs are also required to demonstrate that a manufacturer's failure to warn was a proximate cause of a plaintiff's injury, or, put differently, that a different or additional warning would have resulted in a different outcome—namely that the plaintiff's prescribing physician would *not* have prescribed the drug. *See, e.g.*, *Eck v. Parke, Davis & Co.*, 256 F.3d 1013, 1018 (10th Cir. 2011); *Thomas v. Hoffman-LaRoche, Inc.*, 949 F.2d 806, 812 (5th Cir. 1992); *Jones v. Walter Kidde Portable Equip., Inc.*, 16 F. Supp. 2d 123, 125 (D. Mass. 1998); *Mazur v. Merck & Co., Inc.*, 742 F. Supp. 239, 262 (E.D. Pa. 1990).

For generic drug manufacturers, the Supreme Court has concluded that all failure-to-warn claims are preempted, having rejected the argument that a generic drug manufacturer could have offered a stronger label because federal law "demand[s] that generic drug labels be the same at all times as the corresponding brand-name drug labels." *Mensing*, 564 U.S. at 618. Moreover, because generics may be readily substituted for brand-name drugs (or the reverse), plaintiffs are unsuccessful in establishing proximate causation.

Whether biosimilar manufacturers will enjoy the same preemption defenses to bar failure-to-warn claims remains to be seen, but an examination of both the overall regulatory framework governing biosimilar labeling and decisional law involving generic drugs is instructive. On June 2, 2015, after the FDA's 351(k) approval of Sandoz's Zarxio, another manufacturer, AbbVie, submitted a citizen petition to the FDA seeking clarity on proper biosimilar labeling. AbbVie argued, in pertinent part, that the FDA's actions in connection with Zarxio implied that the FDA would adopt a "same labeling" approach for biosimilar products—the same approach used for generic drugs—and that such an approach was inadequate since, unlike generics, biosimilars are not identical to their reference products. *See* AbbVie Inc. Citizen Pet., Docket No. FDA-2015-P-2000 (June 2, 2015), https://www.regulations.gov/#!documentDetail;D=FDA-2015-P-2000-0001. As AbbVie explained:

> Biosimilars are not generic drugs and should not be labeled like generic drugs. [Certain additional information] is necessary to enable rational and informed prescribing decisions regarding these complex products, to avoid potentially unsafe substitution of biosimilars and reference products, and the combat widespread misconceptions among prescribers about biosimilars and their relationship to reference products. Without this information, biosimilar labeling will not reflect the unique licensure provisions established by the BPCIA and will be materially misleading in violation of the FDCA and FDA regulations.

Id. at 1.

In particular, AbbVie requested that the FDA require that the approved labeling for biosimilar products include the following:

(a) A clear statement that the product is a biosimilar, that the biosimilar is licensed for fewer than all the reference product's conditions of use (if applicable), and that the biosimilar's licensed conditions of use were based on extrapolation (if applicable);

(b) A clear statement that FDA has not determined that the biosimilar product is interchangeable with the reference product (if applicable); and

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(c) A concise description of the pertinent data developed to support licensure of the biosimilar, along with information adequate to enable prescribers to distinguish data derived from studies of the biosimilar from data derived from studies of the reference product.

Id.

After AbbVie's submission, a number of pharmaceutical companies and other interested organizations submitted their own comments, most supporting the petition, or at least requesting transparent labeling procedures for biosimilars. *See, e.g.*, Genentech, Inc. Cmt. on AbbVie Inc. Citizen Pet., FDA-2015-P-2000-0009 (Aug. 27, 2015), https://www.regulations.gov/document?D=FDA-2015-P-2000-0009; Amgen Inc. Cmt. on AbbVie Inc. Citizen Pet., FDA-2015-P-2000-0005 (July 20, 2015), https://www.regulations.gov/document?D=FDA-2015-P-2000-0005. On December 1, 2015, the FDA issued an interim response, stating only that it had been "unable to reach a decision on [the] petition because it raises complex issues." Interim Response Letter

from FDA Ctr. for Drug Eval. to AbbVie Inc. (Dec. 1, 2015), https://www.regulations.gov/document?D=FDA-2015-P-2000-0010.

In March 2016, the FDA took the first step toward clarifying the issues surrounding proper biosimilar labeling, issuing a draft guidance on the subject—although notably, it applies only to non-interchangeable biosimilars—which, despite the FDA's actions concerning Zarxio, departed somewhat from the implicated "same labeling" approach. *See* FDA, *Labeling for Biosimilar Products: Draft Guidance* (Mar. 2016) (*Labeling for Biosimilar Products*), http://www.fda.gov/downloads/drugs/ guidancecomplianceregulatoryinformation/guidances/ucm493439.pdf. The draft guidance provides some initial clarity about the information that biosimilar manufacturers are required to include in their product labeling and has some important implications for litigation involving biosimilars.

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First, of course, biosimilar labeling—the same as the labeling of all pharmaceutical drugs—should contain adequate directions for use and specific approved indications, only offer comparisons or superiority claims that are supported by substantial evidence and clinical data, and not otherwise be false or misleading.

Second, specific to the nature of the product, biosimilar labeling should include a clear statement that the product is a biosimilar. *See id.* at 8–9. Manufacturers may also be wise to state explicitly that a product is *not* an interchangeable to avoid any risk of confusion. It is important that prescribers and pharmacists alike understand the applicable level of biosimilarity since the BPCIA has created a two-tiered structure of biosimilarity. Indeed, omitting such information could be found to be misleading or to suggest that a biosimilar could be substituted for its reference product, thus increasing the risk of inappropriate product swapping. Furthermore, although the draft guidance explicitly states that it does not apply to interchangeable products, manufacturers submitting 351(k) applications for interchangeable products should consider explicitly including such information in any proposed labeling.

Third, biosimilar labeling should clearly identify the indications for which a biosimilar is approved. This is particularly important since the regulatory scheme governing biosimilars contemplates that a biosimilar need not be approved for all of the indications for which its reference product is approved. *See, e.g.*, FDA, *Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009: Guidance* 7–8 (2015) ("*Q. I.7. Can an applicant obtain licensure of a proposed biosimilar product for fewer than all conditions of use for which the reference product is licensed?* A. I.7. Yes, a biosimilar applicant generally may obtain licensure for fewer than all conditions of use for which the reference product is licensed."). Providing such information will reduce the risk that a physician prescribes a biosimilar for an indication for which only the reference product—but not the biosimilar itself—is approved. *See, e.g.*, *Labeling for Biosimilar Products*, *supra*, at 7–9.

Fourth, biosimilar labeling should include a description of the data supporting licensure that is detailed enough for prescribers to distinguish between studies of the biosimilar itself and studies of the reference product. This should also address, to the extent it applies, whether the indications for which a product is licensed were based on extrapolation. Prescribers require such information to avoid any risk that the drug profile of a reference product could be confused with that of the biosimilar.

Following the issuance of its draft guidance, on July 12, 2016, the FDA further clarified labeling questions surrounding biosimilars in denying the citizen petitions of AbbVie and others. *See* Letter from FDA to AbbVie *et al.* (July 12, 2016). While the FDA's response letter primarily denied the petitions without comment, treating them as public comments on the draft guidance and reserving them for further consideration when finalizing the final guidance, the FDA took the significant step of directly addressing AbbVie's assertions that the FDA was promoting the "same labeling" approach for biosimilars. *Id.* at 4–6. Wrote the FDA:

> AbbVie's arguments that FDA applied a "same labeling" approach to the Zarxio… approved labeling lack merit. *FDA does not believe that the "same labeling" requirement for abbreviated new drug applications described in section 505(j) of the FD&C Act apples to products licensed under section 351(k) of the PHS Act.…* As described in the draft biosimilars labeling guidance, the agency's finding of safety and effectiveness for the reference product, as reflected in its FDA-approved prescribing information, may be relied upon to provide health care practitioners with the essential scientific information needed to facilitate prescribing decisions for the proposed biosimilar product's labeled conditions of use. Nevertheless, it may be appropriate to make certain product-specific modifications in the biosimilar's prescribing information.… Although the prescribing information [the biosimilars in question] closely resemble the prescribing information for their reference products in many key aspects, those similarities reflect the relevance of certain information in the reference product labeling to the biosimilar product, as well as the further consideration that biosimilar product labeling that is consistent with the reference product labeling to the extent appropriate should more clearly convey FDA's conclusion that the two products are highly similar and that there are no clinically meaningful differences between the products. Such similarities do not mean that FDA applied a "same labeling" approach.

Id.

While the FDA's draft guidance and denial letter represent important first steps in addressing the substance of a complete

and adequate biosimilar label and at least clarify that the FDA does not apply and will not adopt a "same labeling" approach for biosimilars, they still do not definitively resolve the question of whether failure-to-warn claims against biosimilar manufacturers might be preempted as a matter of law. Viewing the Supreme Court's treatment of failure-to-warn claims against generic drug manufacturers, particularly *Mensing*, 564 U.S. at 618, as guidance on how courts might treat similar claims against biosimilar manufacturers, it is tempting to conclude that such claims should also be preempted since there cannot be any "clinically meaningful differences" between a biosimilar and its reference product. *See* 42 U.S.C. §262(i)(2) (2012). However, as noted above, the FDA's draft guidance for labeling of biosimilar products explicitly contemplates that a biosimilar label, while akin to that of the reference product, should contain "appropriate product-specific modifications" and "need not be identical" to the text of the reference product labeling. *See Labeling for Biosimilar Products*, *supra*, at 3, 5. Moreover, the draft guidance makes clear that biosimilar labels "should reflect currently available information necessary for the safe and effective use of the biosimilar product," noting specifically that "[a]ll holders of marketing applications for drugs (including biological products) have an *ongoing obligation* to ensure that their labeling is accurate and up to date." *Id.* at 5 & n.12 (emphasis added). This language, combined with the FDA's clear statement in its July 12 letter that the same labeling standard does not apply to biosimilars, signify that the FDA not only has rejected the "same labeling" approach used for generic drugs but also may well subject biosimilar manufacturers to a "changes being effected" (CBE)-type requirement such as that applicable to manufacturers of brand-name drugs. *See* 21 C.F.R. §201.56(a)(2) (2015). *See also* 21 C.F.R. §314(c) (2015). Accordingly, at least for now, the availability to biosimilar manufacturers of a preemption defense will depend in part on whether courts decide that the "highly similar" and "no clinically meaningful differences" requirements for biosimilars are sufficiently comparable to the "same as" requirement for generics.

Perhaps more compelling for counsel attempting to determine whether preemption will bar failure-to-warn claims against biosimilar manufacturers is whether manufacturers may unilaterally strengthen their biosimilar labels to comply with both state and federal law. Since the current regulatory framework for biosimilars does not prohibit biosimilar manufacturers from unilaterally amending their labels to strengthen warnings—and, indeed, as mentioned above, appears explicitly to state that biosimilar manufacturers have a responsibility to do so—plaintiffs are likely to argue that preemption should not apply and that preemption of failure-to-warn claims in the generic drug context is inapposite. *Cf. Wyeth v. Levine*, 555 U.S. 555, 568–73 (2009) ("On the record before us, Wyeth has failed to demonstrate that it was impossible for it to comply with both federal and state requirements. The CBE regulation permitted Wyeth to unilaterally strengthen its warning, and the mere fact that the FDA approved Phenergan's label does not establish that it would have prohibited such a change.").

In sum, because biosimilar manufacturers are permitted—and indeed have been provisionally instructed—to ensure that their labels are accurate and up to date, and because biosimilar labels are not subject to the same statutory "sameness" protections as generic drug labels, counsel must remain hypervigilant of failure-to-warn claims against biosimilar manufacturers, for which the *per se* preemption defense enjoyed by generics may not be available.

Given these doubts about the viability of a preemption defense to failure-to-warn claims, biosimilar manufacturers must take care to include all pertinent safety information in their labels. While the FDA has been slow to address fully the proper labeling of biosimilars (and may even be contributing to false and misleading labeling of biosimilars, as AbbVie's Citizen Petition suggests), a biosimilar manufacturer should take care to propose labeling in the course of a 351(k) submission that truthfully and accurately describes the biosimilar product and avoids any risk that end users will be misled. In so doing, a biosimilar manufacturer will also create a robust administrative record that may be useful should future litigation arise.

Notably, the FDA has made clear that its draft guidance for biosimilar labeling applies only to standard biosimilars (and not to interchangeables), so defense counsel should remain abreast of the FDA's forthcoming pronouncements on interchangeable labeling, including whether the FDA may still adopt a "same labeling" approach for interchangeables. Although the FDA's July 12 letter takes the position that the "same labeling" approach does not "appl[y] to products licensed under section 351(k)"—which section governs both standard biosimilars *and* interchangeables, it's unclear whether the FDA intended to include interchangeables in that statement given that its draft guidance does not apply to interchangeables and that the biosimilars implicated in AbbVie's Citizen Petition were not interchangeables. But even if the FDA does not ultimately adopt the "same labeling" approach for interchangeables that is used for generics, interchangeable manufacturers are still more likely to have a stronger preemption argument than standard biosimilar manufacturers because, just as they may with generic pharmaceuticals, pharmacists may freely substitute interchangeable biosimilars with their reference products without the prior approval of the prescribing physician. Accordingly, defense counsel may have an easier time arguing that interchangeables are more akin to generics, especially since the substance of an interchangeable label is rendered effectively moot by its

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ability to be freely substituted (discussed more below). Nevertheless, it remains to be seen whether interchangeable biosimilar manufacturers will have greater success in mounting a preemption defense to failure-to-warn claims than standard biosimilar manufacturers.

Interchangeable biosimilar manufacturers not only may have a stronger preemption defense to failure-to-warn claims than standard biosimilar manufacturers but they also may enjoy a stronger proximate causation defense, an essential element of every failure-to-warn claim, given the statutory substitution feature available to pharmacists. A failure-to-warn claim fails if a plaintiff cannot establish that additional warnings would have altered a physician's decision to prescribe a drug, as previously mentioned. As expected, this proximate cause requirement has proved to be a death knell for failure to warn claims against generics: Since generics and brand-name drugs may be substituted for one another without intervention of the prescribing physician, the generic label (which must be the same as that of the brand-name drug in any case) is, arguably, of no utility to a prescribing physician making a risk-benefit assessment. Similarly, since interchangeables and reference products may also be freely substituted without intervention from the prescribing physician, it follows that an interchangeable's label is also of no utility to a prescribing physician; accordingly, without proof of reliance on a specific interchangeable label, a plaintiff cannot establish proximate cause. In turn, plaintiffs' failure-to-warn claims against interchangeable biosimilar manufacturers will likely fail as a matter of law.

The defenses of preemption and lack of proximate causation—both of which represent generally established defenses for generic manufacturers facing failure-to-warn claims—may not be available to certain biosimilar manufacturers facing similar claims.

In sum, the defenses of preemption and lack of proximate causation—both of which represent generally established defenses for generic manufacturers facing failure-to-warn claims—may not be available to certain biosimilar manufacturers facing similar claims. Interchangeable biosimilar manufacturers may enjoy greater protection from those defenses, but defense counsel should carefully assess the type and features of the biosimilar at issue before concluding whether these defenses may be available to ward off such a claim.

Rise of the Manufacturing Defect Claim?

Because biosimilars, unlike conventional pharmaceuticals, are composed of large-molecule natural resources rather than pure chemical substances with known structures, there is an inherent risk of deviation from the intended design. Accordingly, defense counsel should be prepared for plaintiffs to allege manufacturing-defect claims in the biosimilar context with greater regularity than in product liability litigation involving conventional pharmaceutical drugs. In pleading a manufacturing-defect claim, a plaintiff alleges, among other things, that a product or group of products "departs from its intended design even though all possible care was exercised in the preparation and marketing of the product." Restatement (Third) Torts: Prod. Liab. §2(a) (Am. Law. Inst. 1998). Biosimilars present unique quality assurance challenges given the complexity of the manufacturing process, thus making them more vulnerable to manufacturing-defect claims. Nonetheless, there are a number of unresolved issues that will determine the success of manufacturing-defect claims against biosimilar manufacturers.

First, it remains to be seen whether courts will interpret the concept of "intended design" with the understanding that biosimilar products are inherently variable given the way in which they are manufactured. If courts are deferential to that fundamentally imperfect process, it's conceivable that they may conclude that certain small variations among batches of a product are insufficient to constitute "defects" within the spirit of the law governing manufacturing-defect claims. Instead, courts may require a plaintiff to demonstrate, for example, that the alleged variations fell outside the scope of normal biosimilar variability, in addition to demonstrating, of course, that any deviation was responsible for the alleged injury.

Second, given the inherent variability in biosimilar products, it is likely that increased accountability will be placed on biosimilar manufacturers to ensure quality assurance in the production of such drugs. In particular, manufacturers must pay particular attention to the oversight procedures in place so that a manufacturer, in the face of future litigation, may demonstrate that it undertook all reasonably available methods for ensuring consistency and accuracy in the manufacture of a product.

Experience with claims involving vaccines provides some insight into how courts may treat manufacturing-defect claims against biosimilar manufacturers. The federal law and regulations subject both vaccines and biosimilars to the same regulatory scheme. *See* 42 U.S.C. §262(a), (i), (k) (2012); 21 C.F.R. §601.2(a) (2015). That scheme includes the submission of an application for, and issuance of, a license that "spells out the manufacturing method that must be followed and the directions and warnings that must accompany the product." *See Bruesewitz v. Wyeth LLC*, 562 U.S. 223, 237 (2011) (citation omitted). Accordingly, the Supreme Court has explained with respect to vaccines that

> [d]eviations from the license thus provide *objective evidence of manufacturing defects* or inadequate warnings. Further objective evidence comes from the FDA's regulations… that pervasively regulate the manufacturing process, down to the requirements for plumbing and venti-

lation systems at each manufacturing facility. Material noncompliance with any one of them, or with any other FDA regulation, could cost the manufacturer its regulatory-compliance defense.

Id. (emphasis added) (citations omitted).

Given the overlapping regulatory scheme for vaccines and biosimilars, it follows that the same is likely true for biosimilars. Manufacturers of such drugs should therefore be prepared for plaintiffs to assert aggressively manufacturing defect claims, even if manufacturers retain strong defenses to those claims.

False and Misleading Promotion Claims: Clarity Is Key

Marketing claims may become more prominent against non-interchangeable biosimilar manufacturers (because the FDA does not allow automatic substitution for them) when they choose to market their products actively via drug representatives or other means. While generic drug manufacturers have generally been immune to such claims since generics are copies of brand-name drugs, and accordingly, they require no promotion, standard biosimilar manufacturers may wish to advertise and market their drugs. Those manufacturers must view their promotional activities in the same way that brand-name drug manufacturers view their comparable activities, and they must take care not to overstate the safety and efficacy of their biosimilar products lest they fall prey to false or misleading promotion claims.

Claims arising out of a pharmaceutical manufacturer's promotional activities can take many forms. They could take the shape of fraud and misrepresentation claims, including consumer fraud, fraudulent misrepresentation, fraudulent concealment or omission, or negligent misrepresentation claims. *See*, *e.g.*, Cal. Bus. & Prof. Code §§17200-17210 (West 2008); Mass. Ann. Laws ch. 93A, §§1–11 (LexisNexis 2012); 56 N.J. Stat. Ann. §§56:8-1, 56:8-2 (West 2012); N.Y. Gen. Bus. Law §349 (McKinney 2012); 73 Pa. Cons. Stat. Ann. §§201-1–201-9 (West 2008); *In re Wright Med. Tech. Inc., Conserve Implant Prod. Liab. Litig.*, 127 F. Supp. 3d 1306 (N.D. Ga. Aug. 31, 2015); *Drake v. Allergan, Inc.*, 111 F. Supp. 3d 562 (D. Vt. May 22, 2015). Or they might manifest themselves as civil claims brought by the government under the False Claims Act or the FDCA. *See, e.g.*, 21 U.S.C. §§352, 353(c), 360(e) (2012); 31 U.S.C. §§3729–3733 (2012).

Specific examples of false and misleading promotion by pharmaceutical manufacturers that have been subject to litigation include, but are not limited to, (1) downplaying the risk of a drug; (2) failing to include risk information prominently in a print advertisement; (3) failing to discuss life-threatening risks; (4) exaggerating the efficacy of a drug or using inaccurate superlatives; (5) advertising or promoting a drug for non-approved indications; (6) making claims unsupported by clinical studies, especially those cited in the advertisement in question; and (7) using comparisons to similar products and making claims that a drug is superior to similar products. In the context of false and misleading advertising, manufacturers should treat biosimilars *no differently* than traditional pharmaceuticals or biological products. Put simply, it is incumbent upon manufacturers to avoid engaging in these "red flag" behaviors to avoid providing any false or misleading information in their advertising and promotional materials.

But even more specific to biosimilars, manufacturers should also apply the same principles to their promotional materials and activities that they apply to their labeling. In other words, manufacturers should ensure that promotional materials or activities include the following:

- Directions for use, specific approved indications, and comparisons or superiority claims that are supported by substantial evidence and clinical data;
- A clear statement that the product being promoted or advertised is a biosimilar, as well as a description of what that means;
- An explicit statement that the product is (or is *not*) an interchangeable to avoid any risk of confusion;
- A clear identification of the indications for which the biosimilar is approved; because a biosimilar need not be approved for all of the indications for which its reference product is approved and because plaintiffs continue to actively pursue offWlabel marketing claims, this is particularly important since it is conceivable that such claims could arise if a biosimilar is promoted for an indication for which only its reference product is approved; and
- A description of the data supporting licensure that is detailed enough for prescribers to distinguish between studies of the biosimilar itself and studies of the reference product.

Biosimilar manufacturers should adhere to these recommendations in promoting and advertising biosimilars if they wish to reduce the likelihood that plaintiffs are able to identify actionable false advertising or promotion claims against them.

Experience with claims involving vaccines provides some insight into how courts may treat manufacturing-defect claims against biosimilar manufacturers.

Conclusion

While the FDA still has considerable work to do to establish a complete regulatory framework for biosimilar products—both standard and interchangeable—an analysis of existing FDA guidance and comparable decisional law involving other products already in the marketplace makes clear that biosimilar manufacturers could begin to face claims that have, in comparison, fallen out of favor against both brand-name and generic drug manufacturers. At the same time, however, biosimilar manufacturers may enjoy defenses to many of those claims that are shared by generic manufacturers—especially depending on how the FDA resolves to treat interchangeable biosimilars compared to non-interchangeables. Accordingly, defense counsel must remain hypervigilant of forthcoming FDA action on biosimilars and continue to review analogous decisional law in formulating best practices for defending against inevitable product liability claims involving biosimilars.