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Biosimilars and the Mensing Product Liability Shield: A Primer for Patent Litigators

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As any patent litigator who tries Hatch-Waxman cases knows, a generic drug has to have the same label as the branded reference listed drug ("RLD"), with very limited exceptions.[1] This essentially bright-line rule has clarified Hatch-Waxman disputes, where a generic manufacturer's product label, together with the rest of its Abbreviated New Drug Application, limits what the generic manufacturer can market. Thus, the label itself can be dispositive of the issue of infringement.[2] Unbeknownst to many patent litigators though, the "same labeling" requirement for generic drugs has also significantly impacted products liability litigation by shielding generic drug manufacturers from a variety of state law tort claims. This shield, based on federal preemption, was established by the United States Supreme Court in its landmark case *PLIVA, Inc. v. Mensing*,[3] and *Mensing*'s progeny in federal and state courts.

With the passage of the Biologics Price Competition and Innovation Act ("BPCIA") in 2009 and the FDA's approval in March 2015 of Sandoz's Zarxio® product, the first licensed biosimilar product in the United States, the pharmaceutical industry and its patent attorneys have been primarily focused on how to maneuver through the complexities of the new regulatory framework, and how (if at all) to engage in the "patent dance."[4] However, the impending flood of new biosimilar products[5] may also bring a flurry of products liability cases. Products liability litigators may need to consider important differences between generic drugs and biosimilars to determine whether *Mensing* applies to biosimilars.

Although the BPCIA was enacted for many of the same purposes as the Hatch-Waxman Act, such as to streamline the regulatory approval process and to facilitate competition with lower cost alternatives, the statutory schemes differ in ways that affect how generic drugs and biosimilars reach the market and how they are sold. For instance, unlike the Hatch-Waxman Act, the BPCIA does not contain a corresponding "same labeling" requirement, which means that a biosimilar product's label could be substantively different than the label of the reference listed product ("RLP"). Based on the "same labeling" requirement for generic drugs, generic drug manufacturers have successfully relied on *Mensing* preemption to defeat various state law claims. Biosimilar manufacturers, however, may need to consider if and how the BPCIA's lack of a "same labeling" requirement (and any FDA regulation or guidance on biosimilar labeling, which the FDA has yet to release) may impact the availability of *Mensing* preemption. In addition, while pharmacists can automatically substitute a generic drug for the RLD, biosimilars will not qualify for automatic substitution unless they are deemed "interchangeable" by the FDA.[6] Manufacturers of non-interchangeable biosimilars may therefore choose to actively market their products, which can potentially lead to failure-to-warn or false advertising claims. Thus far, generic drug manufacturers have generally been able to ward off these claims based on established defenses, such as federal preemption or lack of proximate causation.

While the focuses of Hatch-Waxman and products liability cases are distinct, patent litigators and products liability litigators may counsel the very same pharmaceutical company clients and may have to decipher some of the same statutory and regulatory schemes that apply to product labels, interchangeability, and the content of pharmaceutical products. To service their clients most effectively, these lawyers should work collaboratively and keep apprised of the legal and regulatory issues that they each may face. The aim of this article is to help pharmaceutical patent litigators appreciate some of the issues surrounding products liability that may arise in the unfamiliar and somewhat uncertain legal landscape of biosimilars.

I. Biosimilar Labeling: *Mensing* Preemption of Failure-to-Warn Claims

State law tort claims based on insufficient warnings in generic pharmaceutical product labels, i.e., "failure-to-warn"

claims, are preempted under the United States Supreme Court's decision in *PLIVA, Inc. v. Mensing*.[7]

As noted above, the Hatch-Waxman Act requires a generic pharmaceutical manufacturer to provide a label that is the same as the branded reference drug label. Based on this federal "sameness" requirement, the Supreme Court in *Mensing* held that a generic company would violate federal law if it changed its version of the FDA-approved brand label to satisfy a state law duty to properly warn.[8] In other words, it is "impossible for [generic drug manufacturers] to comply with both their state-law duty to change the label and their federal law duty to keep the label the same."[9] In this way, there is a conflict between state and federal law, and the state law duty is preempted by federal law.[10]

The Supreme Court also rejected any claim that a generic drug manufacturer can unilaterally change its labeling under various federal procedures. For instance, the Court held that generic drug companies cannot use the "changes-being-effected" process to unilaterally change their labeling, nor can they send "Dear Doctor" letters to provide additional information to physicians above and beyond what is already stated in the brand label.[11] Moreover, the only mechanism by which generic drug companies purportedly could achieve a change in the package insert—to propose or ask the FDA for assistance in effecting a change—would not in itself have satisfied any state law duty to provide adequate labeling.[12] Thus, the federal requirement that generic labels must have the same label as the reference listed branded product generally[13] preempts failure-to-warn claims.

But, will similar preemption principles bar failure-to-warn claims against biosimilars? Because the BPCIA does not require the same labels for a biosimilar and the RLP, and since the FDA has yet to promulgate any regulations or release final guidance on biosimilar labeling, the answer is unclear.

Take the Zarxio® product as an example. The Zarxio product is Sandoz's biosimilar of Amgen's Neupogen® (filgrastim) product. The FDA and Sandoz agreed that the Zarxio product's label should be "essentially the same" as the Neupogen product label, the FDA gave the Neupogen product label to Sandoz to use as template for its Zarxio product, and the FDA instructed Sandoz to highlight and justify any changes it made to the Neupogen product label, much in the same way justification would be required if the Zarxio product were a generic drug approved under the Hatch-Waxman Act.[14] Although the FDA and Sandoz agreed about the labeling for the Zarxio product, the pharmaceutical industry has raised questions about whether the "same labeling" approach is appropriate for biologics, and the FDA still has not issued any formal guidance on biosimilar labeling.[15]

Under *Mensing*, the key question is whether "essentially the same" is comparable to the "same as" requirement under Hatch-Waxman, such that preemption would apply. *Mensing*'s reasoning leaves open an argument that only a federal requirement of identical labels can have preemptive effect on state law failure-to-warn claims. Without a requirement that the labels be the same, the generic manufacturer could arguably comply with both federal law and a state law duty to provide adequate warnings. In particular, *Mensing* notes that a generic manufacturer cannot even strengthen a warning without the brand moving first, which may not be the case with biosimilars, even where the FDA requires a label that is "essentially the same as" the brand label. In other words, it might not be impossible for biosimilar manufacturers to comply with both federal and state law, as biosimilar manufacturers might be able to amend their product labels unilaterally to strengthen warnings if necessary to satisfy state tort law standards.

Because federal law arguably does not require the Zarxio product's label to be the same as that of the Neupogen product, hypothetical tort plaintiffs could argue that *Mensing* preemption would not apply to failure-to-warn claims based on its label. Looking ahead, if the FDA were to require a particular biosimilar to copy the RLP's label, it might be that *Mensing* preemption applies in that case even though the overall regulatory framework allows for unilateral changes.

II. Biosimilarity vs. Bioequivalence: *Bartlett* Preemption of Design Defect Claims

Since *Mensing*, courts have further strengthened the applicability of federal preemption to state tort law claims against generic pharmaceutical manufacturers. In *Mutual Pharm. Co. v. Bartlett*, the United States Supreme Court expressly reaffirmed *Mensing*, and additionally held that design defect allegations against a generic drug manufacturer, like allegations that directly challenge a generic drug's labeling, are preempted by federal law.[16] The Supreme Court reached this conclusion because, to avoid state law design defect liability, a generic drug manufacturer would either have to change a pharmaceutical product's design or its labeling from that approved by the FDA for the brand-name medication, neither of which is permissible under federal law.[17] As the Supreme Court explained, "redesign [is] not possible . . . [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."[18] Thus, such state law requirements that conflict with federal law are preempted and "without effect."[19] Subsequently, numerous federal and state courts have applied *Bartlett* in rejecting plaintiffs' design defect claims against generic drug manufacturers as preempted.[20]

To obtain approval, a biosimilar applicant must provide data showing, among other things, that the product "is highly similar to the reference product notwithstanding minor differences in clinically inactive components," that "the biological product and reference product utilize the same mechanism or mechanisms of action for the condition or conditions of

use prescribed, recommended, or suggested in the proposed labeling," and that "the route of administration, the dosage form, and the strength of the biological product are the same as those of the reference product."[21] Due to the complexity of their structure, manufacture, and characterization, however, biosimilars are not required to be chemically or clinically identical to the RLP. Since there is no federal "sameness" requirement that the active substance in the biosimilar be identical to that in the RLP, unlike the Hatch-Waxman framework for generic drugs, tort plaintiffs may argue that *Bartlett* preemption should not apply to design defect claims based on biosimilar products. Again, because the federal regulatory framework under the BPCIA allows for differences between an RLP and its biosimilars, biosimilar manufacturers will need to consider whether *Bartlett* preemption is available to bar state law tort claims for design defects.

III. No Automatic Substitution: Failure-to-Warn and False Advertising Claims

As discussed above, pharmacists cannot automatically substitute biosimilars to the same extent that they can automatically substitute generic drugs. This means that to provide a patient with a biosimilar that the FDA has not deemed interchangeable, a physician will normally need to explicitly prescribe the biosimilar for the patient, or else the patient will receive the RLP. In contrast, if a physician prescribes a small molecule drug, a pharmacist typically can unilaterally substitute the RLD with the generic version of the drug. As a result, biosimilar manufacturers may choose to actively market their biosimilar products, whereas generic drugs are generally not marketed. These realities may have two consequences in terms of product liability claims against biosimilar manufacturers.

First, in many cases, generic drug manufacturers have been able to defend themselves from failure-to-warn claims by successfully challenging proximate causation, an essential element of a tort claim. In the generic drug context, a typical fact pattern is as follows: A physician prescribes the patient a branded drug product. The patient goes to the pharmacy to fill that prescription, and the pharmacist substitutes a generic product due to insurance plan requirements and/or to save the patient money on co-pays. The patient, therefore, is only ever exposed to the generic product even though the physician had originally prescribed the branded product. The patient is injured and later files a product liability suit against the generic manufacturer on a failure-to-warn theory. In these cases, at least to the extent the failure-to-warn claim is not already barred under a preemption theory, a proximate cause defense may further shield the generic manufacturer from liability. Because the physician only prescribed the brand drug, the physician likely relied only on the brand label in making his or her prescribing decision. The physician breaks the chain of causation between the generic product and the alleged injury. The patient-plaintiff, therefore, cannot establish proximate causation between the generic's product label and the injury.[22] In order to establish proximate causation, the patient-plaintiff would have to demonstrate that the physician reviewed the generic's product label and relied upon that label in making the prescribing decision.

On the other hand, because only interchangeable biosimilars can be automatically substituted for the RLP, in order for the patient to be exposed to a non-interchangeable biosimilar product the physician must have prescribed the biosimilar and not the RLP. In these circumstances, tort plaintiffs may argue that the proximate cause defense seen in generic drug cases should not be available to biosimilar manufacturers.

Second, because biosimilar manufacturers cannot rely on automatic substitution for increased prescriptions of their products, these companies may find it necessary to actively market their products to physicians and patients, in much the same way that branded pharmaceutical products are marketed. As a result, if a biosimilar manufacturer were to actively market its product, that product may be subject to false advertising claims. These claims are often challenged by generic manufacturers because generic products generally are not marketed or advertised.

IV. Conclusion

Biosimilars present a complex, new obstacle for regulators, courts, pharmaceutical companies, and litigators to tackle. The pharmaceutical industry and patent litigators are awaiting FDA guidance and regulations on biosimilar labeling, naming, and interchangeability because those issues will impact how new biosimilars will be prescribed, sold, and litigated under the BPCIA. Those issues may also have implications down the road for biosimilar manufacturers' potential liability for failure-to-warn, design defect, and false advertising claims. Because of some key differences between the BPCIA and the Hatch-Waxman Act, litigators defending biosimilar manufacturers may need to get creative and think outside of the *Mensing* box. Still, the overriding similarity of both Acts' objectives to streamline the drug approval process and allow for smoother market entry of bioequivalent pharmaceutical products may prompt courts to modify established products liability doctrines, or create new ones, that extend to biosimilar manufacturers the same kind of protections that are available to generic drug manufacturers.

(Endnotes)

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[1] *See* 21 U.S.C. § 355(j)(2)(A)(v) ("An abbreviated application for a new drug shall contain … information to show that the labeling proposed for the new drug is the same as the labeling approved for the listed drug referred to in clause (i) except for changes required because of differences approved under a petition filed under subparagraph (C) or because the new drug and the listed drug are produced or distributed by different manufacturers[.]"). In limited situations, a generic manufacturer, can revise or remove information that is in the reference product's label, provided that such removal has no impact on the safety or efficacy of the drug. *See id*.; 21 U.S.C. § 355(j)(2)(A)(viii); 21 C.F.R. § 314.127(a)(7).

[2] *See*, *e.g*., *Bayer Schering Pharma AG v. Lupin, Ltd*., 676 F.3d 1316, 1326 (Fed. Cir. 2012) (holding that a generic drug could not infringe a method of treatment claim where the reference product's label did not suggest that the drug was safe and effective for the claimed use).

[3] 131 S. Ct. 2567 (2011).

[4] *See generally Amgen Inc. v. Sandoz, Inc*., 794 F.3d 1347 (Fed. Cir. 2015).

[5] On February 9, 2016, the FDA's Advisory Committee overwhelmingly supported approval of Celltrion's infliximab product, a biosimilar of Janssen's Remicade® product, which makes it seem likely that the FDA will soon approve a second biosimilar in the United States. *See* Celltrion Press Release, *FDA's Arthritis Advisory Committee Recommends Approval of Celltrion's CT-P13, a Proposed Biosimilar Infliximab, for All Eligible Indications* (Feb. 10, 2016), http://celltrion.com/en/company/notice_view.asp?idx=481&code=ennews.

[6] *See* 42 U.S.C. § 262(i)(3) ("The term 'interchangeable' or 'interchangeability', in reference to a biological product that is shown to meet the standards described in subsection (k)(4), means that the biological product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product."); *see also* 42 U.S.C. § 262(k)(4).

[7] 131 S. Ct. 2567 (2011).

[8] *Id*. at 2578.

[9] *Id*.

[10] *Id*.

[11] *Id*. at 2575-76.

[12] *Id*. at 2578.

[13] Some courts have allowed plaintiffs to proceed on narrow failure-to-warn theories that the generic pharmaceutical manufacturer allegedly failed to update its label to match a strengthened branded product label. In these circumstances, courts have held that *Mensing* does not require dismissal of the so-called "failure-to-update" claim because it was not impossible for the generic pharmaceutical manufacturer to have changed its label to match the branded label. *See*, *e.g*., *Fulgenzi v. PLIVA, Inc*., 711 F.3d 578, 584 (6th Cir. 2013).

[14] *See* Administrative and Correspondence Documents for BLA # 125553, Memorandum of Meeting Minutes (Nov. 19, 2013), at 16-17, and General Advice Letter (Feb. 6, 2015), at 6, *available at* http://www.accessdata.fda.gov/drugsatfda_ docs /nda/2015/125553Orig1s000AdminCorres.pdf.

[15] In June 2015, AbbVie filed a Citizen Petition challenging the FDA's use of the "same labeling" approach for the Zarxio product, which was supported by comments from Amgen Inc. and Genentech Inc. and opposed by comments from Momenta Pharmaceuticals, Inc. and Sandoz. *See* FDA Citizen Petition Docket ID: FDA-2015-P-2000, *available at* http://www.regulations.gov/#!docketDetail;D=FDA-2015-P-2000. In December 2015, other industry groups filed an additional Citizen Petition asking the FDA to adopt a "same labeling" approach for biosimilars (*see* FDA Citizen Petition Docket ID: FDA-2015-P-4529, *available at* http://www.regulations.gov/#!docketDetail;D=FDA-2015-P-4529); while in January 2016, other industry groups asked the FDA to adopt a dissimilar approach (*see* FDA Citizen Petition Docket ID: FDA-2015-P-5022, *available at* http://www.regulations.gov/#!docketDetail;D=FDA-2015-P-5022).

[16] 133 S. Ct. 2466, 2470 (2013).

[17] *Id*. at 2474-76.

[18] *Id*. at 2475.

[19] *Id*. at 2476-77.

[20] *See*, *e.g*., *In re Fosamax (Alendronate Sodium) Prods. Liab. Litig. (No. II)*, 751 F.3d 150, 165 (3d Cir. 2014); *Drager v. PLIVA USA, Inc*., 741 F.3d 470, 476 (4th Cir. 2014); *In re Isotretinoin Litig*., No. ATL-L-1321-09, 2013 WL 3483813, at *5-6 (N.J. Super. Ct. June 28, 2013).

[21] 42 U.S.C. § 262(k)(2); *see also* 42 U.S.C. § 262(k)(4) (describing additional requirements for an interchangeability determination).

[22] *See*, *e.g*., *Fullington v. Pfizer, Inc*., 720 F.3d 739, 747 (8th Cir. 2013) (no causation on failure-to-update claim where plaintiff's physician "wrote a prescription for the reference listed drug, Reglan, which a pharmacist then filled with metoclopramide" and plaintiff's "prescribing physician relied on information provided by the manufacturer of the reference listed drug, which included the updated warning"); *Bell v. Pfizer, Inc*., 716 F.3d 1087, 1097-98 (8th Cir. 2013) (where "[Plaintiff's] physician prescribed Reglan—not generic metoclopramide," finding no causation on failure-to-update claim because "the causal link between [plaintiff's] injury and [generic manufacturer's] admitted failure to incorporate the 2004 label change, if any, was broken"); *Huck v. Physicians Grp*., No. LACV018947, Order, at 8-9 (Iowa Dist. Ct. Sept. 24, 2015) ("[B]ased on the undisputed facts that neither Huck nor either of her physicians ever read or relied on PLIVA's package insert, any other material provided by PLIVA or any communication from PLIVA[,] . . . PLIVA is entitled to summary judgment on the ground that PLIVA's failure to adopt the 2004 sentences was not a cause of Huck's injuries.").