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Exploring The FDA's Clarification On Biosimilar Labeling

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In general, there are two types of drugs: (1) small-molecule chemical compounds; and (2) large-molecule biologics. Most drugs available today are small-molecule compounds where generic manufacturers are able to effectively duplicate the active pharmaceutical ingredient (API) in the branded drug. It is, however, impossible for manufacturers to duplicate large-molecule biologic products exactly, as even chemically identical biologic products may produce different effects in the body because of the unique structural organization pattern of the proteins. As a result, companies looking to replicate a branded biologic must instead use slightly variant living organisms or processes to create a biosimilar; a biologic that is highly similar, but not an exact duplicate, of an existing biologic approved by the U.S. Food and Drug Administration.

Under the current regulatory scheme, generic small-molecule drug manufacturers must show that the labeling proposed for a generic drug is the same as the labeling approved for the approved brand-name drug. The 2010 Biologics Price Competition and Innovation Act (BPCIA), which paved the way for the introduction of biosimilars in the United States, does not include this "same label" requirement for biosimilars. Nor does the BPCIA outline how the labeling of biosimilar products will be regulated.

The FDA approved the first biosimilar in the United States — Zarxio, a biosimilar of Neupogen — in March 2015. The FDA's approach to labeling this product, however, left many in the industry with questions (and concerns) about how the FDA might approach the labeling of biosimilars in the future. In light of this uncertainty, the FDA released a draft guidance entitled "Labeling for Biosimilar Products: Guidance for Industry" on March 31, 2016.

FDA's Initial Approach to Biosimilar Labeling

Publicly available information from the FDA's review and approval of Zarxio shows that Sandoz (the manufacturer of Zarxio) and the FDA came to an agreement that the label for Zarxio and its reference biologic "should be essentially the same." The FDA even provided Sandoz with a copy of the label for the reference product, Neupogen, to use as a template, and instructed Sandoz to track any changes it suggested making to the label in using it for Zarxio. The FDA also asked Sandoz to explain and justify its suggested changes — essentially the same process undertaken by applicants seeking to market generic versions of small-molecule drugs.

Following the approval of Zarxio, some urged the FDA to abandon the "same label" approach and push for more product-specific labeling for biosimilars. For example, AbbVie Inc. submitted a petition to the FDA in June 2015 illustrating how labeling a biosimilar in the same way as a reference product (as the FDA allowed with Zarxio) could distort the safety and efficacy profile of the biosimilar. AbbVie's petition highlighted that, for example, the Zarxio label contained the exact same data on antibody formation as the label for Neupogen (and simply replaced the references to "Neupogen" with "filgrastim," the generic product name). AbbVie noted this was troubling in light of the fact that: (1) the label for Neupogen clearly stated that its data on antibody formation should not be compared to "other products;" and (2) Sandoz had data to suggest that antibody formation with Zarxio was different from antibody formation observed in patients taking Neupogen. AbbVie suggested that health care practitioners may draw more accurate conclusions about the risks and benefits of a biosimilar product if biosimilar-specific data was included in a biosimilar's label.

March 2016 FDA Draft Guidance

Although the draft guidance contains only nonbinding recommendations, it provides some indication on the FDA's current views relating to biosimilar labeling. The highlights of the draft guidance recommendations are as follows:

- **Overall Approach.** The FDA anticipates that the text in a biosimilar label will generally be similar to the text in the reference product's labeling. Drug manufacturers are advised to incorporate "relevant data and information from the reference product labeling, with appropriate product-specific modifications."

- **Clinical Data.** Generally speaking, information and data from a clinical study of a biosimilar product should not be included in the biosimilar product label unless necessary to inform safe and effective use by a health care practitioner.

- **"Biosimilarity Statement."** Labeling should include a statement making clear that the drug is a biosimilar, and the reference product of the biosimilar should be identified.

- **Name References**. The name of the biosimilar should be referenced in portions of the labeling that specifically relate to the biosimilar, but the name of the reference product should be used when providing information relating to clinical studies or data deriving therefrom that relate only to the reference product. In portions of a label that relate both to a biosimilar and a reference product, including label sections listing contraindications, warnings and precautions, and adverse reactions, the generic name of the reference product followed by the word "products" should be used.

- **Updating Safety Information.** The draft guidance explicitly states that the biosimilar product application holder "must promptly review all adverse drug experience information" and must "take steps to change the content of its product labeling" on an ongoing basis, and does not condition the change in content on the reference holder's label in any way.

- **Immunogenicity.** A statement that is the same or similar to the following is required to appear in the first paragraph of the "adverse reactions" subsection of a biosimilar label, and must precede immunogenicity data based on the reference product labeling:

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparisons of the incidence of antibodies to [reference product's proper name] in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Draft Guidance Product Liability Implications

In the draft guidance, the FDA continues to voice a preference for avoiding the inclusion of data specific to a biosimilar product, but has taken the concerns of critics (like AbbVie) into account by allowing the inclusion of product-specific data, if necessary to properly inform a health care professional on the safety or efficacy of a given product. The draft guidance recommends that "in the biosimilar product labeling, applicants incorporate relevant data and information from the reference product labeling, with appropriate product-specific modifications." In addition, the FDA's requirement in the draft guidance that all biosimilar products contain the disclaimer pertaining to immunogenicity described above in the "adverse reactions" portion of their labeling directly addresses AbbVie's concerns relating to the possible misinterpretation of product-specific immunogenicity data.

The initial inquiry in many product liability lawsuits begins with an examination of a drug's label to determine whether the warnings provided by a drug's manufacturer were accurate or adequate. As such, if a biosimilar's label merely recites information about the reference biologic product and does not include specific information pertaining to risks 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 and/or accurate.

The FDA's outlined approach of allowing data specific to a biosimilar product to be included in the product's label when necessary to inform a health care professional about the safe and effective use of a product will likely help curb plaintiffs' success in prevailing on failure-to-warn claims, as long as biosimilar manufacturers make the necessary additions and modifications relating to safety and efficacy to the labels of their reference products that the draft guidance seems to allow. Thus, manufacturers should continually — not just at the time a proposed label is initially submitted to the FDA — examine whether or not the inclusion of product-specific clinical data should be added to a label in order to ensure the information presented is accurate and adequate to inform the prescriber.

As currently written, the draft guidance also suggests that a preemption defense to certain product liability claims may not be available to biosimilar manufacturers. As outlined above, federal regulations mandate that generic small-molecule drugs employ the same labeling as their reference drugs, and also generally prohibit them from making unilateral changes to a label after approval. Given this regulatory scheme, the United States Supreme Court has held that federal law preempts failure-to-warn claims against generic drug manufacturers. Pliva v. Mensing, 131 S. Ct. 2567 (2011).

The draft guidance, however, states that biosimilar product manufacturers will be permitted to change their labels unilaterally in response to post-marketing adverse event reports. In fact, the FDA warns that a biosimilar may be found misbranded if its labeling is not kept up-to-date and accurate. As such, attorneys for biosimilar manufacturers are less likely to be successful when asserting a preemption defense, assuming the relevant provisions of the draft guidance are adopted.

Conclusion

The draft guidance provides the FDA's current position on a number of issues relating to biosimilar labeling, but those recommendations have not yet been adopted. Comments on the draft guidance were required to be submitted by June 3, 2016, and as outlined above, could have far-reaching implications on later product liability litigation.

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