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A Brave New World for Biosimilars

How Labeling Requirements May Impact Preemption of Product Liability Claims

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The FDA approved the first biosimilar on March 6, 2015. Although this biosimilar could enter the U.S. market very soon, the FDA has not yet issued guidance for biosimilar product labeling. According to the FDA, the guidelines are due out later this year. A key question—will biosimilar labeling follow the "sameness" requirement that is used for generic drugs? And what are the potential ramifications for product liability claims?

Biosimilars Are Different from Generic Small Molecule Drugs

The current generic drugs on the market are small chemical molecules, typically manufactured through chemical synthesis. A generic version of small molecule drug has an identical chemical structure to its branded counterpart. State laws permit (or in some cases mandate) automatic substitution of the generic for the branded version at the pharmacy level once the generic enters the market. By statute, a small molecule generic drug must have the same labeling as the branded version. As such, the package insert, which provides the diseases and conditions approved for treatment, the mode of administration, dosage, potential adverse effects and the clinical studies performed with the drug, is the same for both the branded and generic versions.

Biosimilars, although sometimes referred to as the "generics" of biologic drugs, have some key differences from their small molecule counterparts. Biologics are generally large complex proteins, produced in and then purified from living cells. Biosimilars are not required to be identical in structure to the original biologic, only "highly similar." Although they have the same protein as the reference biologic, biosimilars may differ in other structural features, such as different sugars or other chemical

groups that are attached to the protein. These structural modifications can influence the activity of the drug, as well as provoke different immune responses when administered to a patient.

Unlike small molecule generics, pharmacists cannot substitute a biosimilar drug for a prescription written for the reference biologic. Whereas a small molecule generic is considered the bioequivalent of the branded version, a biosimilar is not. The currently enacted state laws only allow substitution by biosimilars that have been designated by the FDA as interchangeable. This subclass of biosimilars must meet a higher standard, namely that it will produce the same clinical result as the original biologic in any given patient. Additionally, if the drug is administered multiple times there must be no greater risk of switching between the interchangeable biosimilar and the reference biologic as there would be for only taking the reference biologic. So far, the FDA has not granted interchangeable status to any biosimilars. Therefore, for the currently approved biosimilar and those following in the short-term, physicians will have to specifically name the biosimilar in the prescription for drug to be sold and administered.

The lack of a complete parallel between small molecule generics and biosimilars raises interesting questions concerning potential product liability claims as these drugs come into general use.

Preemption for Small Molecule Generic Drugs

For small molecule generics, the “sameness” requirement for labeling, as well as their automatic substitutability, has provided a shelter for generic manufacturers from failure to warn and design defect claims in product liability.

The Supreme Court explained the division of responsibilities that underlies preemption: the responsibility for the accuracy of the label and adequacy of warnings falls to the branded drug manufacturer, whereas the generic manufacturer must make sure its label is the same as the branded drug. It is an impossibility for generic manufacturers to comply with state laws that impose a duty to provide a safer label because if the generic company changed its label it would violate the federal law mandating sameness with the branded counterpart. This preemption shields the generic manufacturers from state law failure to warn claims.

Design defect claims against generic manufacturers are preempted for similar reasons. The FDA requires that a generic drug have the same active ingredient, dosage form, strength and route of administration as the brand-name version. Once approved, a generic manufacturer cannot change the drug’s formulation, including inactive ingredients. Design defect claims generally depend on the ability of a manufacturer to redesign its product to decrease the risk or increase the benefits over the potential risks of the product. However, as the Supreme Court has explained, this is an impossibility for generics because they must remain identical in chemical structure to their branded counterparts.

Will Failure to Warn and Design Defect Claims Be Preempted for Biosimilars?

Biosimilars present a different set of circumstances from generics. Because the biosimilar is not identical to the reference product, one might surmise that a biosimilar would have a package insert that would differ in some respects from the labeling of the reference biologic.

However, the labeling for the first approved biosimilar suggests that it is following the path of small molecule generics. Although it is not currently approved as an interchangeable, the product label submitted to the FDA closely replicates the package insert for the reference biologic. The label does not identify the drug as a biosimilar. It includes the clinical studies performed with reference biologic. None of the analytical or clinical studies performed with the biosimilar that were used in the FDA application are included on the label.

Will this first biosimilar establish a precedent for identical labeling between biosimilars and the reference biologics? If so, will co-opting the “sameness” of labeling protect biosimilar manufacturers from failure to warn and design defect claims? And finally, will the FDA or other industry pressures push biosimilars away from copycat labeling?

During the FDA approval process, the biosimilar manufacturer generates analytical and clinical data comparing the biosimilar to the reference biologic. This may include comparisons of structural data, as well as pharmacokinetics and pharmacodynamics profiles and even head-to-head clinical trial comparisons. This data reflects the safety and efficacy profile known to the biosimilar manufacturer and the FDA at the time of approval. As it stands now, the current statutes and regulations do not mandate “sameness” of labeling for biosimilars. This data could therefore be included in the initially approved product label.

Differences between biosimilars and the reference biologic may also become apparent through the required post-approval monitoring. It is possible that the type or frequency of adverse events may differ between the biologic and the biosimilar due to their underlying differences in protein modifications. Additionally, because biosimilars are not identical to the reference biologic, this also means that multiple biosimilars for the same drug are not identical to each other and may generate different post-approval data as well. These differences could be reflected through later updates to the biosimilars’ labels.

Currently, no statutes or regulations prevent the biosimilar manufacturer from including biosimilar-specific data or comparison data on the label. As a result, it is possible that the reasoning holding branded pharmaceuticals responsible for adequate warning labels could apply to biosimilars. Specifically, regulations permit the manufacturers of a branded drug to update its label with new safety information. Additionally, even after FDA’s review and approval of the original label, the

manufacturer may strengthen the label with additional safety information. With the permissibility to reflect differences in the labeling between biosimilars and the reference biologic, failure to warn claims could be limited to the specific drug at issue, be it the reference biologic or a particular biosimilar, without liability from one necessarily flowing to the other.

Design defect claims may also be impacted. For small molecule generics, redesign is not possible because it would require a change to the chemical structure of the drug, and thus the drug would no longer be classified as a generic. This line of reasoning does not necessarily apply to biosimilars. Because only the primary amino acid sequence of the protein must be identical, the biosimilar manufacturer may be able to change some features of the chemical structure (e.g., chemical groups attached to the protein). These features may be changed by altering the type of living cells and conditions under which the biosimilar is made and purified. Thus, absent any regulatory barriers, redesign may be possible in some cases and arguments supporting a design defect claim could be made.

What Does the Future Hold?

The question remains as to how the FDA guidelines will shape the labeling of biosimilars and impact the landscape for product liability claims. In the face of the first biosimilar launch, Congress has begun to press for more immediate guidance. However, the final guidelines are not expected until later this year.

In the draft guidelines released February 2012, the FDA suggests that “a clear statement” on the label would be required to advise healthcare providers that the drug “is approved as biosimilar to a reference product for stated indication(s) and route of administration(s)” and to indicate whether or not it had been approved as interchangeable. The draft does not provide any guidance as to whether biosimilar-specific data would be required or even could be included on the label.

Industry pressure may sway the FDA away from the “sameness” requirement that governs generic labeling. A survey of 400 physicians conducted in March 2015 by the Alliance for Safe Biologic Medicines suggests that physicians may have different expectations for biosimilar labeling. An overwhelming percentage (90%) of those surveyed considered it important that the label identify the drug as a biosimilar. Over 80% wanted the label to include data demonstrating how the biosimilar was analytically as well as clinical highly similar to the reference product. Other surveys in the healthcare industry suggest that many want to see head-to-head clinical comparisons between the biosimilar and the reference biologic. If these industry preferences point the direction for biosimilar labeling, biosimilars could stand on their own when facing failure to warn and design defect claims.

Even if the “sameness” of labeling does prevail for biosimilars, new FDA rules could alter the landscape. The FDA has proposed to change the current rules to allow generic manufacturers to

submit labeling changes, for example, based on updated adverse event data. The generic would be required to notify the branded manufacturer of the proposed label change. The change to the label of the generic would then trigger a similar change required for the branded drug as well as any other generic forms of the drug. This two-way flow of information between generic and branded drugs has been met by a great deal of resistance in the industry and so far, the rule has not been implemented. Should something similar be proposed for biosimilars, sorting out which label changes should be common to all of the biosimilars and the reference biologic due to the shared protein structure and which labeling changes are due to non-shared features may be quite a challenge.

Given the new issues that biosimilars bring to the industry, product liability law will likely evolve as the U.S. market moves into this brave new world.