



IP: Bring On The Biosimilars

A section of the Affordable Care Act could cost biosimilar manufacturers and reference sponsors significant time and money

BY BRYAN VOGEL

Despite all the headlines, there's one aspect of the Supreme Court's decision on the constitutionality of the Affordable Care Act that didn't get much coverage. The court's approval of the entire act means that the Biologics Price Competition and Innovation Act of 2009 (BPCIA) within the law now goes into full effect. BPCIA sets out a regulatory and dispute resolution framework for follow-on biologics or biosimilars inspired by the one the Hatch-Waxman Act uses for small-molecule generics. But, the fundamental differences that exist between biological products (large molecule drugs) and small molecule drugs and the process for approval and dispute resolution under the BPCIA means that reference product sponsors and biosimilar manufacturers will find themselves in uncharted and potentially time-consuming and costly waters.

Unlike small-molecule drugs covered by the Hatch-Waxman Act, biologics are generally produced using a living system or organism. As a result, BPCIA has an application and approval process that requires significant up-front time and investment from the biosimilar manufacturer. The BPCIA provides for two categories of follow-on biologics: biosimilars and "interchangeable" biologic products. A biosimilar application must contain data showing that a proposed follow-on biologic is "highly similar" to the reference product, notwithstanding minor differences in clinically inactive components. The application must demonstrate the required biosimilarity through analytical studies, animal studies and a human clinical study or studies that are sufficient to demonstrate the follow-on biologic is "safe, pure and potent." While the Food and Drug Administration (FDA) may elect to waive any of these requirements, it is completely within the FDA's discretion and, thus, unclear which, if any, of these requirements may be waived.

During the application process, the biosimilar applicant may use a newly developed assessment protocol to seek guidance from the FDA to discuss the kind of clinical study or other similar studies that may be needed. Still, the very real possibility that a biosimilar manufacturer may have to put its proposed follow-on biologic through a clinical study or other similar studies means significant increased time and costs to bring a biosimilar to market.

In addition to demonstrating "high similarity," a successful biosimilar must:

- Have the same mechanism of action as the reference product
- Share the previously approved condition(s) of use
- Employ the same route of administration, strength and dosage form as the reference product
- Have facilities that meet standards designed to ensure the biosimilar is "safe, pure and potent"

A biosimilar applicant can also (optionally) seek to show that its follow-on biologic is "interchangeable" with the reference product. Interchangeability means that the follow-on biologic "may be substituted for the reference product without the intervention of the healthcare provider who prescribed the medication." To be interchangeable the biosimilar applicant must show that that follow-on biologic "can be expected to produce the same clinical result as the reference product in any given patient" and, if administered more than once, the "risk in terms of safety or diminished efficacy of alternating or switching" between the products is "not greater than the risk of using the reference product without such alternation or switch." BPCIA provides incentives to the first biosimilar applicant to demonstrate interchangeability by providing

a period of exclusivity during which no other product can be deemed interchangeable with the reference product. This period of exclusivity ends on the earliest of:

- One year after first commercial marketing
- If no expedited patent litigation suit is brought against that applicant under the Public Health Service Act (PHSA) § 351(l), 18 months after approval
- If an expedited patent litigation suit is brought against that applicant under PHSA § 351(l), 18 months after final decision on all patents-in-suit (or dismissal)
- If an expedited patent litigation is brought against that applicant under PHSA § 351(l) and still pending, 42 months after approval

After putting its follow-on biologic through all the necessary regulatory steps, a biosimilar manufacturer must then adhere to the process BPCIA lays out for addressing potential patent infringement claims. BPCIA sets out four basic steps for potential patent litigation, including strict guidelines on the timing of information exchanges between the biosimilar manufacturer and the reference product sponsor:

1. Once the FDA notifies a biosimilar manufacturer that its application has been accepted for review, the manufacturer has 20 days to provide confidential access to the reference sponsor of the application and related manufacturing information.
2. Both parties then exchange lists of potentially relevant patents over specified periods. During this process, the biosimilar applicant must provide a statement why the patents will not be infringed, are invalid and/or

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are unenforceable, and the reference sponsor must provide a statement why the patents will be infringed and responses to the biosimilar applicant's statement.

3. The parties then engage in a mandatory negotiation period. If the negotiation is unsuccessful, the parties then must agree to a subset of patents for expedited litigation.
4. The reference sponsor has 30 days after agreement to the subset of patents to bring suit on those patents.

There are penalties on both sides for failure to make the required disclosures. Lack of full disclosure by the biosimilar manufacturer subjects it to the potential of a declaratory judgment action on any patent in the exchanged lists. Reference sponsors that fail to correctly identify patents will have damages or patent enforcement opportunities curtailed. Further, unlike under the Hatch-Waxman Act,

the initiation of patent infringement litigation or success in such litigation does not stay or bar FDA approval.

Though highly detailed, BPCIA's approval and dispute resolution processes are ripe for controversy. The BPCIA does not require the FDA to engage in rulemaking or issue guidance documents. Key concepts remain undefined. Information exchanges must come from individuals with specified roles that may not yet exist within the reference sponsor's organization.

All this uncertainty means that both reference sponsors and biosimilar manufacturers must anticipate and address key strategy considerations and implications long before any biosimilar application is ever filed. Reference sponsors need to consider the role a future biosimilar application will have on patent rights in drafting patents and in any patent enforcement actions inside and outside

the biosimilar arena. Biosimilar manufacturers will need to conduct a thorough review of the patent landscape as part of their up-front risk/benefit analysis to determine whether the possible high rewards that biosimilars promise are worth the time and cost of entry. And every player who decides to proceed will likely need to do so with equal amounts of cash, optimism and caution.

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