

Congress Debates The Future Of Generic Biologics

Congress is currently considering legislation that establishes a regulatory pathway to allow the U.S. Food and Drug Administration (FDA)



STEVEN H. SKLAR

to approve generic versions of biological drug products known as “generic biologics” or “biosimilars.” Many argue that lower-cost generic versions of biologics are needed due to the explosive growth in their use – around \$100 billion in 2010, up from \$50 billion in 2005. To treat debilitating illnesses like cancer and rheumatoid arthritis, these biologic medicines can

cost patients tens of thousands of dollars each year.

Congress has its work cut out. Any legislation will undoubtedly seek to achieve an appropriate balance between the incentive to invest in the discovery of tomorrow’s life-saving medicines and today’s need for affordable drugs. This article reviews the key aspects of S. 1695 recently introduced in the Senate.

S. 1695, the “Biologics Price Competition and Innovation Act of 2007,” was introduced on June 26, 2007. This bill follows earlier legislation from February, 2007 (H.R. 1038 and S. 623) directed to this same issue. The Senate Health, Education, Labor, and Pensions (HELP) Committee has passed S. 1695 for consideration by the full Senate. No counterpart version has been introduced in the House to date.

The approval of biological products is governed by the Public Health Service Act (PHSA), specifically 42 U.S.C. § 262. S. 1695 establishes requirements for the submission of a biologics license application (BLA) to obtain FDA approval to market a generic biologic.

Definition of Biosimilarity v. Interchangeability

Under the proposed amendments to the PHSA, a generic biologic product is defined in terms of either its “biosimilarity” or “interchangeability” to a previously approved (reference) biologic drug product. A biologic is “biosimilar” if there is an absence of clinically meaning-

ful differences between the two products in terms of safety, purity, and potency. Data sufficient to establish biosimilarity must come from non-clinical, analytical studies, animal studies and clinical studies (including an assessment of immunogenicity). A biologic is considered “interchangeable” with the reference drug if the two products are (1) biosimilar and (2) expected to produce the same clinical result in any given patient.

Exclusivity

One of the more controversial provisions in S. 1695 relates to the exclusivity period afforded to the reference biologics. Specifically, an application for a generic biologics cannot receive final FDA approval for 12 years after the date on which the reference product was first licensed. This 12-year period of marketing exclusivity does not exist under the Hatch-Waxman Act. Moreover, an application for a generic biologic product cannot even be submitted to FDA until 4 years after the date of approval of the reference product.

On the generic side, S. 1695 provides companies with an incentive to conduct clinical studies to establish interchangeability with the reference drug product. Exclusivity is awarded to the first applicant to receive an FDA determination of interchangeability. This is like the 180-day exclusivity awarded under the Hatch-Waxman Act to the filer of the first Abbreviated New Drug Application (ANDA) that contains a Paragraph IV certification. Exclusivity is only awarded for establishing interchangeability to the reference biologic drug product, not biosimilarity.

The exclusivity period awarded to the first interchangeable product precludes approval of a second interchangeable product until the earliest of the following four events:

- (1) 1 year after the first commercial marketing of the first interchangeable biological product;
- (2) 18 months after either a court decision or dismissal (with or without prejudice) of an action for patent infringement instituted under the Act;
- (3) 42 months after approval of the first interchangeable biological product if patent litigation brought

- pursuant to the Act is ongoing; or
- (4) 18 months after approval of the first interchangeable biological product if no patent infringement action has been filed pursuant to the Act.

These provisions involve concepts of both triggering (upon commercial marketing or a court decision) and forfeiture (following FDA approval) taken from the 180-day generic exclusivity provisions in the Hatch-Waxman Act.

Patent Information and Patent Infringement Litigation

The proposed legislation seeks to promote early resolution of patent infringement claims before generic biologics enter the market. The bill does not establish a central publication containing patents covering approved BLAs (in contrast to the Orange Book for New Drug Applications). Instead, relevant patent information is exchanged on a confidential basis between the generic BLA filer and the reference product sponsor as a prelude to an action for patent infringement.

Initially, the generic BLA filer must provide a copy of its entire application and other information describing its manufacturing process to the reference product sponsor. This information is protected by confidentiality restrictions. Next, the reference product sponsor has 60 days to provide a list of patents for which a claim of infringement could reasonably be asserted. The generic BLA filer then provides a detailed statement of the factual and legal basis (on a claim-by-claim basis) that all such patents is invalid, unenforceable or will not be infringed. This provision is similar to the patent certification notice letter that must be sent following the filing of a Paragraph IV certification. Alternatively, the generic BLA filer may indicate that it does not intend to begin commercial marketing until the expiration of one or more patents.

The reference product sponsor must respond to the generic BLA filer's statement within 60 days with its own detailed statement of the factual and legal basis (on a claim-by-claim basis) that such patents will be infringed including a response to the allegations of invalidity and unenforceability raised. The pre-litigation process ends with a negotiation between the generic BLA filer and reference product sponsor regarding specific patents that remain in dispute. This negotiation

involves the simultaneous exchange of lists of patents that both sides believe should be the subject of an infringement action.

Whether or not there is an agreement over the particular patents at issue, the reference product sponsor must bring an action for infringement within 30 days of the final determination of the extent of patents in dispute. Jurisdiction for the action exists under new 35 U.S.C. § 271(e)(2)(C) which makes the filing of a generic BLA an act of infringement (similar to the filing of an ANDA) for those patents identified in the required lists of relevant patents exchanged between the generic BLA filer and the reference product sponsor.

A critical difference between the proposed legislation and the Hatch-Waxman Act is the effect of an infringement action on FDA approval of the generic application. Final FDA approval of a BLA for either a biosimilar or interchangeable biologic is not tied in any way to patent litigation. That is, there is no 30-month stay of approval of the generic BLA preventing the marketing of the generic biologic product while the lawsuit proceeds.

Under S. 1695, a reference product sponsor is penalized for not bringing a patent infringement action in a timely matter. If the reference product sponsor brings suit after the required 30-day period, then the only remedy available for infringement is a reasonable royalty. No injunction keeping the generic biologic off the market may be obtained in this situation. Even if an infringement action is timely filed, this same limited remedy of a reasonable royalty is only available where the action is dismissed without prejudice (and subsequently refiled) or not prosecuted in good faith. No action for infringement may be filed pursuant to 35 U.S.C. § 271(e)(2)(C) over a patent that should have been disclosed by the reference product sponsor during the exchange of information with the generic BLA filer.

Steven H. Sklar is a partner in the intellectual property law firm Leydig, Voit & Mayer, Ltd. Mr. Sklar is a registered patent attorney focusing on patent litigation and counseling in the biotechnology and pharmaceutical fields including, in particular, issues relating to the Hatch-Waxman Act. He can be reached at 312-616-5600 or at ssklar@leydig.com.



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