PUBLICATION

Health Care Reform Legislation Allows for Approval of Follow-On Biologic Products

Authors: J. Carter Thompson, Jr.
May 4, 2010

Introduction. On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act (PPACA). Title VII, Subtitle A of the PPACA established the "Biologics Price Competition and Innovation Act of 2009" (the BPCIA). The BPCIA creates a new regulatory program to be administered by the U.S. Food and Drug Administration (FDA) that authorizes the FDA to license what are called "follow-on biologics."

Background and Purpose. The Act represents Congress's desire to replicate for follow-on biologics what it had achieved for the generic drug industry under the Drug Price Competition and Patent Term Restoration Act of 1984 (P.L.98-417), also known as the Hatch-Waxman Act. Under Hatch-Waxman, Congress intended to (1) create savings in the health care system by allowing the FDA to approve comparatively cheaper generic medications deemed by the FDA to be equivalent to brand name drug medications; and (2) promote new, innovative brand name drugs in the U.S. by allowing brand name companies to recover extensive research and design (R&D) and clinical trial costs by obtaining patent extensions of their pharmaceutical breakthrough products.

In enacting the BPCIA, Congress hopes the approval of follow-on biologics will provide comparable savings as potential substitutes to the biologic brand-name "reference" products they seek to replace. Consistent with the patent extension provisions of Hatch-Waxman, BPCIA is intended to promote innovative biologic products by giving manufacturers a 12-year market exclusivity term for approved brand name biologic products.

Despite their similar purpose, Hatch-Waxman and BPCIA are distinct in how they approve "generic" drugs on the one hand and "follow-on biologics" on the other. Under Hatch-Waxman, generic drug companies are able to gain FDA approval by demonstrating that their product is chemically identical to the brand-name drug by relying on FDA's previous finding of safety and effectiveness applicable to the original brand-name drug that the generic seeks to replace. This means that generic drug companies need not incur the R&D and clinical trial costs of their brand name competitors, and are better able to sell their products in the market place at lower prices. However, follow-on biologic manufacturers do not have the same cost advantage as their generic counterparts because of the inherent physical nature of biologics. Because of their physical qualities, it is scientifically difficult to prove equivalence between the follow-on and the original biologic reference product. As stated by the Congressional Research Service:

In contrast to chemical drugs, which are small molecules and for which the equivalence of chemical composition between the generic drug and innovator drug is relatively easy to determine, a biologic, such as a protein, is much larger in size and much more complex in structure . . . In many cases, current technology will not allow complete characterization of biological products and additional clinical trials may be necessary before FDA would approve a follow-on biologic.[1]

Thus, unlike generic drugs that rely on prior FDA findings regarding safety and efficacy, follow-on biologics must incur greater costs in testing and clinical trials in order to prove to the FDA their similarity to the original brand-name reference product.

FDA Regulatory Pathway for Approval. The BPCIA amends the Public Health Service Act (PHSA) by creating a regulatory "pathway" for the approval of follow-on biologics by the FDA. To do so, the BPCIA amends the definition of "biological product" under the PHSA to specifically add "protein (except any chemically synthesized polypeptide)" to the list of characteristics that make up biologic products subject to FDA approval and licensing. The revised definition of "biological product" reads as follows:

[T]he term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.

To make clear that the PHSA now gives the FDA authority to approve reference biologic products as well as follow-on biologics, the BPCIA adds to the PHSA the definition of "biosimilar" and "biosimilarity" as follows:

The term "biosimilar" or "biosimilarity," in reference to a biological product that is the subject of [a follow-on biologic] application, means—

- (A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
- (B) there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.

FDA Product Approval Standards for Follow-on Biologics. To obtain licensing approval under the BPCIA, a follow-on biologic must first demonstrate to the FDA "biosimilarity" with the reference product. To demonstrate such "biosimilarity," the applicant must submit information containing preclinical studies; analytical studies demonstrating that the follow-on biologic is "highly similar to the reference product;" and clinical data "sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed and intended to be used."

In addition, the applicant must demonstrate to the FDA the follow-on biologic will use the same mechanism for the conditions of use prescribed in the reference product's labeling; that the route of administration, the dosage form and the strength of the follow-on biologic are the same as those of the reference product; and the facility in which the follow-on product is manufactured, processed, packed or held meets standards designed to assure that the biological product continues to be safe, pure and potent.

The applicant is also required to submit publicly available information regarding the FDA's previous determination that the reference product is safe, pure and potent and may include any additional information with respect to the reference product (including relevant publicly available information).

The FDA is permitted to waive those data requirements it deems unnecessary to making a determination of biosimilarity between the follow-on biologic and the reference product.

Approval of Follow-On Biologics Determined by FDA to Be "Interchangeable." The BPCIA allows an applicant for a follow-on biologic to seek a determination by FDA of "interchangeability" between the follow-on biologic and the reference product. The term "interchangeable" is defined to mean that the follow-on biologic product

may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.

For a follow-on biologic to be classified as one that is interchangeable, the follow-on must not only demonstrate that it is "biosimilar" with the reference product but that it can be expected to produce the "same clinical result" as the reference product. For those follow-on products seeking classification as "interchangeable" which are administered more than once on a patient, the applicant must demonstrate that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."

Data Exclusivity for Reference Biologics. Under the BPCIA, any FDA-approved follow-on biologic "may not be made effective" until the date that is 12 years from the date on which the reference product was first licensed by the FDA. According to BPCIA, this is a period of time during which a follow-on manufacturer, in preparation of an application for approval of a follow-on biologic, is restricted from referring to data submitted in the original reference product manufacturer's application to FDA for approval of the brand-name product. Nor can a follow-on biologic applicant submit an application until four years from the date the reference product was licensed. If a reference product has been designated an orphan drug, an application for a follow-on biologic or interchangeable product may not be filed until the later of (1) the seven-year period of orphan drug exclusivity, or (2) the 12-year period established by the BPCIA.

To help ensure that reference product companies could not obtain additional 12-year exclusivity periods for changes in already-approved biologics that do not provide significant clinical benefits to patients, the BPCIA includes a number of minor changes in an approved product that are not eligible for 12 years of exclusivity as follows: (1) any change that can be accomplished through filing of a supplemental application rather than a new application; (2) new indications; (3) changes in dosage form, strength or route of administration; or (4) modifications in molecular structure that are not shown to improve the safety or effectiveness of the original product.

Data Exclusivity for First-Time Interchangeable Follow-On Biologics. The BPCIA legislation allows for a period of market exclusivity for the follow-on biologic that is the first to be established "interchangeable" with a particular reference product. The length of market exclusivity ranges anywhere from one year from the date of first commercial marketing to 18 to 42 months from the date of FDA licensing depending on whether the applicant is sued for patent infringement and the outcome of such litigation. According to the legislative history of the BPCIA, during this time frame, a non-interchangeable follow-on biologic determined by FDA to be biosimilar to the same reference product to which the interchangeable applies may be approved and marketed.[2]

Proposed Guidance and Public Comment. The FDA is authorized – but not required – to publish proposed guidance for public comment prior to publication of final guidance on the licensure of a biological product or a class or category of biological products. If guidance is to be developed, a process must be established to allow for public input regarding priorities for issuing guidance. However, the issuance or non-issuance of guidance would not preclude the review of, or action on, an application for a follow-on biologic.

Resolution of Patent Infringement Claims. The BPCIA's approach to handling patent infringement is distinct from the process adopted by Hatch-Waxman. Under Hatch-Waxman, each holder of an FDA-approved brand name drug is required to list in the so-called "Orange Book" the patents the holder believes would be infringed if a generic drug were marketed before the expiration of the patents. The patent infringement process in Hatch-Waxman requires FDA to suspend consideration of the generic drug application in question for 30 months or until the patent in question is found to be invalid or not infringed.

The BPCIA does not adopt Hatch-Waxman's "Orange Book" listing for purposes of patent infringement litigation. Instead, a 180-day process is established that allows the follow-on biologic applicant and the reference product sponsor to exchange information regarding those patents against which the reference product sponsor (or exclusive license holder) could potentially assert a claim of patent infringement and those patents that the reference holder has agreed to license to the applicant (an alternative dispute resolution procedure could be created upon agreement of the two parties). Following "good faith negotiations" on an agreed-upon list of patents and associated claims, the BPCIA creates an expedited litigation procedure. The reference product sponsor must bring suit within 30 days of either the date an agreement is reached on the list of disputed patents or 30 days from the date in which it was formally determined than an agreement could not be reached. Failure to bring a lawsuit in this time frame means the reference product holder risks forfeiting future recovery and royalties. In addition, the follow-on biologic applicant must provide notice to the reference product sponsor 180 days before launching an approved follow-on biologic in order to give the reference product sponsor an opportunity to file for preliminary injunction relating to patents that were initially identified by the reference product sponsor as being potential infringements but were not included on the exchanged list of patents subject to the expedited litigation procedure.

User Fees. Under the BPCIA, current user fees that apply to prescription drugs would apply to follow-on biologic applications. The FDA is authorized to audit the costs of reviewing follow-on biologic applications and alter the user fee structure appropriately. The FDA is required to develop recommendations regarding goals for the review of biosimilar product applications for fiscal year 2013 through fiscal year 2017 and present them to Congress. The recommendations are to be published in the *Federal Register* with a 30-day public comment period, and a public meeting must be held. The recommendations would be presented to Congress by January 15, 2012, and used by Congress to create a permanent user fee structure for the FDA follow-on biologic regulatory approval process.

Effective Dates. The BPCIA went into effect on the date of enactment of the PPACA, March 23, 2010.

Rulemaking. The BPCIA does not require the FDA to issue rulemaking or guidance implementing the legislation. The agency is given broad latitude in defining key terms and concepts under the Act. For example, while the words "biosimilar" and "biosimilarity" are defined in the Act, the definition depends on the agency's interpretation of what is meant by such phrases as "highly similar," "clinically meaningful differences" and the word "interchangeable."

---

1. Judith A. Johnson, FDA Regulation of Follow-On Biologics, Rept. No. RL34045, Congressional Research Service, April 26, 2010.
2. See, H. Rept. No. House Report 111-299, Part 1, To accompany H.R. 3200, the America's Affordable Health Choices Act, 111th Cong., 1st Sess. (2009) at 741.