

The Future Role of Biosimilars and Follow-on Biologics in Health Care

Biosimilars Approval: A Work in Progress

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act), which was signed into law in March 2010, established an abbreviated approval pathway for biological products that are demonstrated to be “highly similar” (biosimilar) to a biological product approved by the agency.¹ BPCI also defines an additional higher standard in which products can be deemed both biosimilar and interchangeable. BPCI provides the necessary framework for approval of biosimilars, but many details of the approval process must be established.

Implementing the provisions of the BPCI Act is a complex undertaking for the Food and Drug Administration (FDA). FDA took a substantial first step in implementing BPCI when it held a public meeting in November 2010, which was covered in the last newsletter. New



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- » A Primer on the Science of Biosimilars
- » Building the Regulatory Framework for Biosimilars
- » Addressing Patient Concerns with the Use of Biosimilars

issues and questions continue to arise; however, FDA can use as a model approaches taken by both the European Union and European Medicines Agency (EMA) as it moves forward.

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A Moving Target: Exclusivity

One of the issues that emerged since the November 2010 public meeting is the exact interpretation of the exclusivity provisions for innovator biologics that fall under BPCI. The source of considerable debate and controversy in the BPCI legislation was the length of exclusivity for innovator biologic products. Proposals ranged from roughly 5 to 14 years of exclusivity. Generic manufacturers, consumer groups, and payers

sought a short exclusivity period to facilitate quicker access to biosimilars. On the other hand, manufacturers of biologics sought the longest possible exclusivity period to protect their interests.

In passing the BPCI Act, the U.S. Congress sought to strike a balance between fostering innovation and facilitating consumer access to lower-cost medica-

tions.¹ Twelve years of exclusivity are granted for an innovator biological, with an additional 6 months if pediatric studies are conducted.² An application for a biosimilar product may not be submitted to FDA for 4 years after approval of the innovator product. One year of exclusivity is granted for the first interchangeable biosimilar.

Consumer groups concerned about the high cost of biologic therapies seek a biosimilar approval pathway to make these therapies more affordable for patients and have criticized the long period of exclusivity for the innovator.^{3,4} Approval of biosimilars could create competition and reduce the cost of biologic therapies.⁵ Payers, including the federal government, are keenly interested in the potential for cost savings from the approval of biosimilars.

Questions recently arose about interpretation by FDA of the term exclusivity.^{6,7} Whether data exclusivity, market exclusivity, or both were intended for the 12-year period after innovator product approval is the subject of debate. Manufacturers of innovator products and some members of Congress contend that the use of innovator drug data by generic drug manufacturers of biosimilar products is precluded for the 12-year exclusivity period, although generic manufacturers could conduct research and submit their own data

for biosimilar products to FDA 4 years after approval of the innovator product.⁶ In this view, innovator products have both market and data exclusivity in the first 4 years after approval, followed by 8 years of data exclusivity but not market exclusivity.⁷

Generic manufacturers of biosimilar products, other members of Congress, consumer groups, and payers contend that the 12-year period is a market exclusivity period, and innovator product data should be made available to generic manufacturers after the 4-year exclusionary term prohibiting submission of an application to FDA for a biosimilar product expires. This translates into 4 years of both market exclusivity and data exclusivity, followed by 8 years of market exclusivity for the innovator.⁷

The debate about the interpretation of exclusivity currently is unresolved. The stakeholders have written to FDA expressing their views and requesting clarification. The final interpretation of the exclusivity provisions within BPCI could have substantial implications on how quickly various biosimilars become available on the market during the next decade. A clarification by FDA or amendment to the law could affect the speed with which biosimilar products enter the market place.



Be sure and check out a new podcast dialog between James Hoffman and Phil Johnson, which was recorded during the recent ASHP Midyear Clinical Meeting in Anaheim. These faculty members discuss what they learned about pharmacist and physician understanding of biosimilars during their speaking engagements in the fall as well as reflect on the FDA Public Hearing on biosimilars, which was held in early November. The podcast interview is available on the initiative website (www.BiosimCentral.org).

Generic Enoxaparin

A generic form of the low molecular weight heparin product, enoxaparin, produced by Sandoz Inc. was approved by FDA on July 23, 2010.⁸ The innovator enoxaparin product, Lovenox (sanofi-aventis U.S., formerly known as Aventis Pharmaceuticals), was approved by FDA in 1993. Although generic enoxaparin has sometimes been referred to as a biosimilar to the innovator product, it is not a biosimilar for a number of reasons. First, from a product standpoint, enoxaparin

is not a therapeutic protein produced from a living system, such as a cell culture. Second, from a regulatory perspective, the innovator enoxaparin product was not approved under a Biologic License Application (BLA). Generic enoxaparin was approved through the existing Abbreviated New Drug Approval (ANDA) process. Third, the approval process for generic enoxaparin was initiated years before BCPI, which uses the term biosimilar, became law. Although generic enoxaparin

is not a biosimilar to the innovator product, it is a complex molecule. Approval of this complex molecule provides important perspectives for the emerging approval process for biosimilars under BPCI.

The approval process for generic enoxaparin was controversial and complicated. Various groups with vested interests suggested that clinical trials would be necessary to demonstrate equivalence with the innovator product.⁹ FDA did not require such trials. Enoxaparin is a complex semi-synthetic biologically-derived product (made from porcine intestinal mucosa) with a mixture of oligosaccharides produced by chemical or enzymatic depolymerization and cleavage of heparin. The complex mixture of oligosaccharides varies in chemical structure and size. Modification of the chemical reaction used for heparin depolymerization can affect oligosaccharide chain size, composition, and sequence and the pharmacokinetics and pharmacodynamics of the enoxaparin product. Various physicochemical and biological assays, including activated partial thromboplastin time and anti-factor Xa and IIa activity, are used to characterize the biological activity and immunogenicity of the product.

In 2003, a citizen petition was submitted to FDA on behalf of the manufacturer of the innovator enoxaparin product questioning the approval criteria for generic enoxaparin and asking that the agency refuse to approve any generic version of enoxaparin based on scientific and legal concerns.¹⁰ After careful evaluation of these concerns, FDA concluded that a generic

version of enoxaparin can be approved based on the following criteria demonstrating that it contains the same active ingredient as the innovator¹¹:

1. Equivalence of heparin source material and mode of depolymerization
2. Equivalence of physicochemical properties
3. Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
4. Equivalence in biological and biochemical assays
5. Equivalence of in vivo pharmacodynamic profile

In approving generic enoxaparin using these criteria, FDA did not require additional clinical studies to demonstrate equivalence with the innovator product in effectiveness or safety. Time will tell whether FDA will need to develop product-specific guidance for biosimilars under BPCI.

If the experience with generic enoxaparin is representative of biosimilars approved under BPCI, it appears that the view of biosimilars and speed of adoption by clinicians will be mixed. For example, many clinicians were quick to prescribe generic enoxaparin while others were far more cautious. As is the case with biologic products, enoxaparin (Lovenox) is expensive and is consistently among the top expenditures in health systems. Thus, it was not surprising that the generic enoxaparin product gained substantial market share in a few short months after it was approved. A similar scenario would be expected for biosimilars.

Implications for Health Care Practitioners and Payers

The provisions of the BPCI Act have important implications for pharmacists, physicians, health systems, and payers in making formulary decisions. Members of pharmacy and therapeutics committees and health system and health plan administrators should carefully consider the FDA guidance in establishing their own criteria for use of biosimilars. Available efficacy, safety, and cost data for biosimilars should be carefully evaluated in the context of criteria for use of biosimilars established in the institution or health plan when making formulary decisions. After biosimilars are adopted for use in an institution or health plan, mechanisms should be established to objectively evaluate the efficacy,

safety, and cost of biosimilar use in specific patient populations.

Safety monitoring through pharmacovigilance activities will be instrumental in ensuring the safe use of biosimilars because of their abbreviated approval pathway and uncertainty about the appropriateness of extrapolating safety and efficacy data from an innovator product to a biosimilar product.

Guidelines for establishing and conducting a pharmacovigilance program are available from the World Health Organization.¹² Pharmacovigilance programs

may be implemented in health systems and by health plans and governmental agencies. Pharmacists and physicians can play an important role in performing the pharmacovigilance functions listed in Table 1 using the methods listed in Table 2.

Risk evaluation and mitigation strategies (REMS) already have been established for innovator biological products, and also will likely be required for biosimilar products. Implementing and managing REMS can place a burden on health care practitioners, health systems, and health plans because of the lack of standardization and time-consuming nature of the requirements. Nevertheless, the use of REMS may provide a proactive strategy for managing safety concerns surrounding biosimilars. The FDA acknowledges the burden associated with REMS and seeks to minimize the burden by standardizing REMS to facilitate integration into health care systems.¹³ Groups, such as the National Comprehensive Cancer Network, have suggested improvements for REMS.¹⁴

Table 1
Pharmacovigilance Functions

- » Detection and study of adverse reactions
- » Measurement of risk
- » Measurement of effectiveness
- » Risk-benefit evaluation
- » Dissemination of information/education to improve prescribing

Table 2
Pharmacovigilance Methods

- » Spontaneous reporting
- » Prescription event monitoring
- » Case control surveillance
- » Record linkage (automated population databases, "data mining")

A Moving Target

FDA Commissioner Margaret Hamburg recently acknowledged that the biosimilars approval pathway is subject to continual change.¹⁴ The science will continue to improve, specifically the ability to characterize complex molecules and more concrete knowledge

regarding the level of evidence that will be required for approval of a biosimilar. Safety will always be a concern such that pharmacists, physicians, and other stakeholders will need to continue to watch for new or different adverse events with biosimilars.

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Continuing Medical Education



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For complete information about educational activities that are part of the 2010-11 Biosimilars Initiative, visit www.BiosimCentral.org. There is no charge for the activities, and ASHP membership is not required.

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