

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

## FDA Approval Pathway for Biosimilar and Interchangeable Biological Products Discussed in Public Hearing November 2-3

A public hearing was held by the Food and Drug Administration (FDA) November 2-3, 2010, to gather input on issues and challenges associated with the implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). This legislation, 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.<sup>1</sup> Various stakeholders, including clinicians who treat patients with biopharmaceutical products and representatives from brand name and generic drug manufacturers, pharmacy benefits management (PBM) companies, academic institutions, and patient and consumer advocacy groups, made presentations about their concerns related to the approval pathway during the two-day hearing. BCPI provides an overall framework for approval of biosimilars. However, many details of BCPI will require FDA action and guidance, which will be closely watched by all stakeholders. This meeting was an important first public action in FDA's process to develop guidance for biosimilars.

Biopharmaceutical products have a larger molecular weight and more complex three-dimensional structure



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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

than traditional drugs.<sup>2</sup> It is more difficult to completely characterize biopharmaceuticals than traditional small-molecule drugs using available physicochemical analytical methods and bioassays. Biopharmaceutical products are heterogeneous and can elicit an immune response, which raises safety concerns.

Reproducibility of the manufacturing process for biopharmaceuticals is an issue because the process affects the quality (e.g., purity, immunogenicity, stability), biologic activity, efficacy, and safety of the end product. Parts of the manufacturing process may be proprietary or protected by patent.

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## Background

In implementing the BPCI Act, FDA seeks to allow the use of established knowledge of a drug, thereby avoiding unnecessary duplication of effort for clinical research and saving time and resources.<sup>1</sup> According to BPCI, FDA has a range of options regarding the amount and types of data to be required for approval of a biosimilar, including analytical (in vitro) studies demonstrating that the biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; animal studies that include assessment of toxicity; and clinical studies that are sufficient to demonstrate safety, purity, and potency in one or more conditions of use for which the reference product is licensed and intended to be used and for which licensure is sought for the biologic product.

Provisions of the BPCI Act establish two standards—one for biosimilarity and the other for interchangeability. BPCI allows FDA approval of a “biosimilar” product if data demonstrate that the product is “highly similar” to the reference (i.e., innovator) product notwithstanding minor differences in clinically inactive ingredients and there are no clinically meaningful differences between the biological product and the reference product in safety, purity, or potency.<sup>3</sup> In addition, to be interchangeable, the biosimilar product must produce the same clinical results as the reference product. When multiple doses are used in a patient, the risk of switching between the biosimilar product and the reference product must not be greater than the risk of using the reference product consistently.

## Different Points of View

All stakeholders at the public hearing urged FDA to use caution in designing the process to approve biosimilars, but the specific approaches advocated varied among different stakeholders. Generic drug manufacturers, who stand to gain financially from the approval of biosimilars, encouraged FDA to establish an approval pathway that would allow for the extrapolation of safety and efficacy data from one biopharmaceutical product to other products, provided that the mechanism of action is well understood and there is scientific justification for data extrapolation.<sup>5,6</sup> Jonah Houts, chairman of the Alliance for Affordable Medicine, a coalition of large employers, consumer groups, prescription drug manufacturers, pharmacies, PBM companies, and plan sponsors whose mission is to expand access to safe and affordable medicines, spoke at the hearing in support of this practice to minimize unnecessary and unethical human testing.<sup>5</sup> Bill Vaughn, a health policy analyst at Consumer’s Union (the independent, nonprofit organization that publishes *Consumer Reports*), noted the high price of biologics, criticized the long period of data exclusivity for the innovator (12 years), and emphasized the need for a biosimilar

### Record of Hearing Available in Video and Transcript Forms

Persons unable to attend the FDA public hearing on a biosimilars approval pathway were able to view and hear the presentations by live webcast. A video recording was made of the hearing, and it will be available for 1 year at <http://www.fda.gov/Drugs/NewsEvents/ucm221688.htm>. A transcript also is available at <http://www.regulations.gov> or in hard copy or CD-ROM form upon submission of a Freedom of Information request. Written requests should be sent to Division of Freedom of Information (HFI-35), Office of Management Programs, Food and Drug Administration, 5600 Fishers Lane, Room 6-30, Rockville, MD 20857.

approval pathway to make biologic therapies more affordable for patients.<sup>5,7</sup> However, others are skeptical that biosimilars will be affordable, even if they cost less than the innovator product.<sup>5</sup>

Brand name drug manufacturers, who stand to lose financially from the approval of biosimilars, cautioned

against data extrapolation and emphasized the need for rigorous comparative clinical trials to ensure the safety and efficacy of biosimilars. Gregory Schimizzi, M.D., a rheumatologist testifying at the hearing, expressed concerns about safety because of the risk of unanticipated immune responses from the use of biosimilar products.<sup>5</sup> Marie Vodicka, Ph.D., Associate Vice President of Scientific and Regulatory Affairs at the Pharmaceutical Research and Manufacturers of America (PhRMA), which represents U.S. pharmaceutical research and biotechnology companies, encouraged FDA to focus on the following principles as the agency develops an approval pathway for biosimilars<sup>8</sup>:

- » Ensure patient access to safe and effective biosimilars;
- » Create a science-based pathway through an open, transparent process; and
- » Encourage innovation and enable additional competition.

To promote patient safety and public health, PhRMA encouraged FDA to establish postmarketing surveillance and risk evaluation and mitigation strategy requirements for biosimilars that are at least as rigorous as those for the innovator product.<sup>8</sup> The group also advocated the use of labeling for each biological product that clearly states the approved indications, whether the product is biosimilar to and interchangeable with other products, and whether supporting clinical data are available for the biosimilar or only the innovator product. Additional clinical and safety information to facilitate prescribing should be included in the labeling, according to PhRMA.

The FDA's goal of balancing the need for increased

competition with the need to preserve incentives for research and development incentives was acknowledged by PhRMA. In her testimony, Dr. Vodicka encouraged the agency to apply the provisions of the BPCI Act in a manner that encourages innovation to expand treatment options for patients.<sup>8</sup>

The Biotechnology Industry Organization (BIO), a group of entrepreneurial companies, state and regional associations, service providers to the industry, and academic centers involved with biotechnology products, shares the concerns of PhRMA about the need for nonclinical and clinical studies to demonstrate biosimilarity and interchangeability, pharmacovigilance to ensure patient safety, and data protection and exclusivity to promote research and development.<sup>9</sup>

Rasmus Rojkjaer, M.D., Ph.D., who spoke on behalf of the Generic Pharmaceutical Association (GPhA), said that its members are focused on gaining approval of high-quality biogeneric medications at prices that are within the grasp of patients in the United States. GPhA's three-step approach would involve comparing the physical and chemical attributes of biosimilars with referenced products, conducting long-standing studies comparing products with appropriate animal or tissue modeling, and lessening the requirements for chemical testing of biosimilars. Dr. Rojkjaer's reasoning is that chemical testing for biosimilars should not be required to the same extent as for new active substances because the patient response to biosimilars will be predictable to a similar degree as expected for originator products that have undergone manufacturing changes.

### **The European Experience**

A framework for approving biosimilars was established in Europe in 2004,<sup>4</sup> and the approval pathway for them in the United States is expected to be similar. Some clinical testing is required for biosimilar product approval by the European Medicines Agency (EMA), the European regulatory counterpart to the Food and Drug Administration (FDA) in the United States, with decisions

about the extent of testing made on a case-by-case basis. Biosimilars of at least three biopharmaceuticals that are relatively easy to make (human growth hormone, epoetin alfa, and granulocyte colony-stimulating factor) have been approved by the EMA. Safety can be a concern.

## Just a First Step

There is no deadline for FDA to establish the pathways for biosimilars approval. The hearing was a first step in the process for creating a framework for approval of biosimilars.<sup>5,10</sup> The exact timetable for approval of the

first biosimilars is unknown, but there is clear interest from various stakeholders in the development of the approval pathway.



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](http://www.BiosimCentral.org)).

### Continuing Pharmacy Education



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

### Continuing Medical Education



The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

For complete information about educational activities that are part of the 2010 Biosimilars Initiative, visit [www.BiosimCentral.org](http://www.BiosimCentral.org). There is no charge for the activities, and ASHP membership is not required.

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