

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

National Initiative on Biosimilars for Physicians and Pharmacists is Underway

ASHP Advantage is conducting an educational series on the future role of biosimilars in health care. This national educational initiative is intended to get physicians and pharmacists up to speed before these biopharmaceuticals are introduced in the U.S. This cutting-edge educational initiative includes the following:

- » Three one-hour web-based continuing education home study activities, including a primer* on the science of biosimilars
- » Live two-hour regional educational activities
- » Live one-hour continuing education webinars
- » Resource Center featuring podcasts, e-Newsletters, and other essential links

*This primer addresses the science behind the development and manufacturing of biologic agents and lays the foundation for a more robust discussion of the patient safety issues surrounding the use of biosimilars. Participants are strongly encouraged to complete the online primer in advance of their attendance at the live continuing education activities, including webinars.

Regional Programs

Physicians and pharmacists in the Washington, D.C., San Francisco, and Chicago metropolitan areas should plan to attend the program entitled "Preparing the Health System for the Introduction of Biosimilars in the United States." The programs are approved for up to two hours of continuing education for physicians and pharmacists.

Register online today

- » October 6, 2010—Bethesda, Maryland
- » October 13, 2010—San Francisco, California
- » November 11, 2010—Chicago, Illinois

Visit www.BiosimCentral.org for a complete listing of activities and resources

Join Your Colleagues for a Webinar

Looking for something to do during lunch? Invite your physician and pharmacist colleagues to join you for a webinar over lunch. For your convenience, each of two one-hour webinars will be presented twice. The webinar entitled "Regulatory Considerations for Biosimilars in the United States: Update on the Status and Future Implications" will take place on Thursday, October 21, 2010, from 1:00 pm to 2:00 pm EDT and these will be repeated on Wednesday, November 3, 2010, from 1:00 pm to 2:00 pm EDT.

A second webinar, "Preparing for Biosimilars: Key Stakeholder and Patient Safety Considerations" will be held on Wednesday, October 27, 2010, from 12:00 pm to 1:00 pm EDT and repeated on Monday, November 15, 2010, from 1:00 pm to 2:00 pm EDT. Complete information about the webinars, including instructions for participating as a group, is available at www.BiosimCentral.org.

FDA to Hold Two-Day Hearing on Approval Pathway for Biosimilar and Interchangeable Biological Products

The U.S. Food and Drug Administration will convene a public hearing on November 2 and 3, 2010 from 8:30 am to 4:30 pm to gather input on issues and challenges associated with the implementation of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act). Individuals who want to present at the public hearing need to register on or before October 11, 2010. Electronic comments will be accepted after the public hearing until the end of the year (December 31, 2010). The public hearing will take place at FDA's White Oak Campus, which is located at 10903 New Hampshire Avenue, Building 31, Room 1503 in Silver Spring, Maryland.

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Care Act (known as the PPAC Act), establishing an abbreviated approval pathway for biological products that are demonstrated to be "highly similar" (biosimilar) to a biological product approved by the FDA.¹ These new statutory provisions are referred to as the BPCI Act. The goal of the BPCI Act is similar to that of the Drug Price Competition and Patent Term Restoration Act of 1984 (known as the Hatch-Waxman Act), which established abbreviated pathways for the approval of small-molecule, chemically-synthesized drug products under the Federal Food, Drug, and Cosmetic Act.¹ The BPCI Act is consistent with the goal of FDA to allow the use of established knowledge of a drug, thereby avoiding unnecessary duplication of effort for clinical research and saving time and resources.¹

Provisions of the BPCI Act allow 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.² To be interchangeable, sponsors must demonstrate that the biosimilar product produces 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.

Much of the debate surrounding FDA approval of biosimilars relates to the fact that biopharmaceutical products have a larger molecular weight and more complex three-dimensional structure than traditional drugs.³ Compared with small molecules, it is more difficult to completely characterize biopharmaceuticals using available physicochemical analytical methods and bioassays. Production of biopharmaceuticals is a complex process involving the harvesting of proteins that are produced by genetically-engineered living host cells. The products are heterogeneous and can elicit an immune response, which raises safety concerns. The manufacturing process affects the quality (e.g., purity, immunogenicity, stability), biologic activity, efficacy, and safety of the end product, so the reproducibility of the process is an issue. Parts of the manufacturing process may be proprietary or protected by patent.

The next newsletter will cover key points discussed at the public hearing.

The Case of Erythropoiesis-Stimulating Agents

Epoetins are the products for which there is the most experience to date. Epoetin alfa, a 165-amino acid glycoprotein manufactured by recombinant DNA technology with the same biological effects as endogenous erythropoietin, is widely used to treat the anemia of chronic renal failure. Two epoetin

alfa products currently are marketed in the United States (Epogen, Amgen; Procrit, Ortho Biotech) with key patents that expire in 2013. At least eight other epoetin alfa products are marketed outside the United States. Pure red cell aplasia (PRCA) characterized by severe anemia during epoetin alfa therapy in

patients with kidney disease has been attributed to the production of neutralizing anti-erythropoietin antibodies.^{4,5} PRCA is an example of a serious adverse event that can occur with biologics. The majority of PRCA cases involved an epoetin alfa product produced and marketed in Europe (Eprex, Johnson & Johnson), suggesting that this product is more immunogenic than epoetin alfa products marketed in the United States because of manufacturing differences. Thus, this product and possibly other

products marketed outside the United States probably will not be considered biosimilar to products currently marketed in the United States. Darbepoetin alfa is another 165-amino acid glycoprotein related to erythropoietin manufactured by recombinant DNA technology that is used in patients with the anemia of chronic renal failure. It is not considered biosimilar to epoetin alfa because it has two additional glycosylation chains and a longer plasma half-life and dosing interval than epoetin alfa.

Botulinum Toxins

Botulinum toxins have a wide variety of non-cosmetic uses for conditions characterized by excessive neuromuscular activity or chronic pain, including the treatment of blepharospasm (involuntary contraction of the eye muscles), strabismus (crossed or misaligned eyes), and cervical dystonia (a neuromuscular disorder involving the head and neck).⁶ There are seven serologically distinct botulinum neurotoxins, two of which (A and B) have been used clinically. The first botulinum toxin product (Botox, Allergan) contained serotype A and was approved by FDA in 1991. A formulation containing serotype B (Myobloc, Solstice Neurosciences) was approved by FDA in 2000. A different formulation of serotype A (Dysport, Ipsen) was used outside the United States for many years, and it recently (2009) was approved by FDA. The agency does not consider the botulinum toxin products biosimilars or interchangeable, even when the serotype is the same, because of important differences in the manufacturing process and formulation that affect clinical use, including dosing. To resolve the considerable confusion surrounding these products, FDA es-

tablished new nomenclature for each botulinum toxin product: (1) onabotulinumtoxinA (Botox, Allergan), (2) rimabotulinumtoxinB (Myobloc, Solstice Neurosciences), and (3) abobotulinumtoxinA (Dysport, Ipsen).

A third botulinum toxin serotype A product, incobotulinumtoxinA (Xeomin, Merz Pharmaceuticals), recently was approved by FDA and will be available in late September.^{7,8} The product is not biosimilar to other botulinum toxin products, including those containing serotype A.

Questions about the interchangeability of biopharmaceutical products will likely persist in the future with the implementation of the BPCI Act. Establishing criteria for the designation of biosimilars with equivalent physicochemical characteristics, biological activity, purity, effectiveness, and safety provides the basis for confident decision making in product selection by clinicians.

References

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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. There is no charge for the activities, and ASHP membership is not required.

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