Biosimilars Issues Document

Updated: August 1, 2014

Summary
The availability and cost of biologic agents has become a critical issue as patents expire on leading biologic products and as public concern increases for better management of rising healthcare costs. While the Biologics Price Competition and Innovation Act (BPCIA) and additional guidance from the US Food and Drug Administration (FDA) on biosimilar development has provided an approval pathway and insight for development of biosimilars, there have been no biosimilar medications approved to date in the US. This document serves to provide an overview of the FDA approval pathway, industry guidance and pending issues surrounding biosimilars within the US market.

Take-Away Points
- A biosimilar is a biological product that is similar to an already approved reference biologic, despite minor differences in clinically inactive components.
- Biosimilars have the potential to enhance competition, lead to better patient access and lower overall healthcare costs.
- The Biologics Price Competition and Innovation Act (BPCIA) created an abbreviated approval pathway for biosimilar products. This is known as the 351(k) pathway.
- European Medicines Agency (EMA) has authorized six unique biosimilar chemicals (total of 17 products), while the FDA accepted the first application for review on July 24, 2014.
- The 351(k) pathway addresses interchangeability, taking approval a step further than the EMA.
- The FDA has addressed the ambiguity of the biosimilar approval process by issuing five detailed guidance documents, although pending issues still exist.
- Express Scripts is closely following this issue and will provide updates as more information becomes available.

Biosimilars Background
Non-biologic medications are made through chemical processes, while biological products are developed from living organisms. Biologic products are used for the treatment of a variety of health conditions. They are usually larger and structurally more complex than small molecule prescription drugs. Most biologics are licensed under the Public Health Service Act (PHS Act) while small molecule prescription drugs are approved under the Food, Drug and Cosmetic Act (the FD&C Act).

A biosimilar is a biological product that is highly similar to a reference biological product and does not contain any clinically meaningful distinctions from the approved reference product in terms of the safety, purity and potency. Until the passage of the Patient Protection and Affordable Care Act in March 2010, no provisions existed to allow approval of biosimilar products based on comparison to already licensed biological products. The BPCIA amended the PHS Act, creating an abbreviated approval pathway for biosimilar and interchangeable versions of the approved products [351(k) applications] and established a 12-year exclusivity period for reference products licensed under PHS Act [351(a)]. Biosimilars may cost 15% to 30% less than their branded counterparts, providing the opportunity for healthcare cost savings.

Under the 351(k) pathway, a biosimilar product may be considered interchangeable with a reference product if additional efficacy and safety data is provided. There is a two step process that must take place. Step 1, a non-interchangeable biosimilar product becomes approved. Step 2, the manufacturer may conduct additional clinical trials to attempt to gain interchangeability status with the reference product. An interchangeable product must meet the requirements of biosimilarity and produce the same clinical result as the reference product in any patient. When switching between an interchangeable biosimilar and biologic reference, safety and efficacy cannot differ between...
products. Only an interchangeable product may be substituted for the reference product without consent from the prescribing health care provider.

To date, the FDA has not approved a biosimilar product. The complexity of the biosimilar approval process has led some sponsors to seek approval with the standard Biologics License Application (BLA). The FDA approved Granix™ (tbo-filgrastim – Teva), which was created as a full BLA copy. The product is similar to Neupogen® (filgrastim – Amgen), but approved under the standard approval package.

On July 24, 2014, Sandoz announced that the FDA has accepted its application for filgrastim, filed under the 351(k) pathway. Sandoz’s application is the first of its kind to be filed and accepted by the FDA. If approved, the product will be a biosimilar to Amgen’s reference product Neupogen®. FDA approval of Sandoz’s biosimilar is expected by Mar. 24, 2015.

**FDA Draft Guidance Documents**

In an attempt to address the ambiguity of the biosimilar approval process, the FDA has issued five draft guidance documents. Below is a description of the currently available guidance documents.

**Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (02/09/12):** This document provides answers to common questions from sponsors during the development of biosimilar products. Three categories are addressed: Biosimilarity or Interchangeability; Provisions Related to Requirement to Submit a BLA for a “Biological Product;” and Exclusivity.

**Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (02/09/12):** This guidance provides the FDA’s stepwise approach to determining biosimilarity. In the “totality of evidence” approach, the FDA will consider structural and functional characterization, nonclinical evaluation, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and clinical safety and effectiveness data. Under the approach, the sponsor should evaluate at each step the extent of uncertainty about the biosimilarity of the proposed molecule and investigate further ways to address that uncertainty.

**Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (02/09/12):** The guidance is intended to provide recommendations on the scientific and technical information of the 351(k) application. The document provides an overview of analytical factors to consider when assessing biosimilarity.

**Formal Meetings between the FDA and Biosimilar Biological Product Sponsors or Applicants (03/29/13):**
The guidance outlined standardized procedures for requesting, preparing, scheduling, conducting and documenting formal meetings with the FDA in regards to biosimilars.

**Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (05/13/14):**
The guidance provides clarification to the 2012 guidance documents, identifying the data the FDA will expect to see in 351(k) applications. In this document, the stepwise process is further established. The document identifies clinical pharmacology studies as the key approach to achieve “totality of evidence”. As in the 2012 draft guidance, the FDA recommends that “extensive and robust comparative structural and functional studies” precede clinical pharmacology studies. The FDA identified three key considerations in comparing a biosimilar to a reference product: exposure and response assessment, evaluation or residual uncertainty and analytical quality and uncertainty. The FDA further recommends that attributes of the biosimilar and reference product be compared through use of a “meaningful fingerprint-like analysis algorithm” to determine the extent of similarity. The FDA stresses required integrity of the bioanalytical methods used in comparison studies. There is also further recommendation for safety, immunogenicity data and critical study design issues. Sponsors are encouraged to meet with the FDA in the early stages of development to discuss clinical pharmacology plans.

Additional guidance is expected to be issued by the FDA this year. The documents will cover interchangeability to a reference product, labeling, reference product exclusivity, and additional questions and answers.

**Biosimilars in Europe**
The European Medicines Agency (EMA) biosimilar regulation differs from the FDA in terms of use of foreign reference products, extrapolation of indications, clinical testing (case by case vs. comparative), interchangeability and naming guidance. The EMA provides product specific guidelines outlining trial requirements demonstrating similarity. Interchangeability is a key difference in guidance. The EMA does not evaluate interchangeability and leaves the decision for substitution to the individual states, while the FDA addresses interchangeability as a second step after a
biosimilar is approved through the 351(k) pathway. Some European states prohibit interchangeability between a biosimilar and its reference product, while others have not addressed the issue. All biosimilars authorized in Europe are distinguished with either a brand name or specific feature in the nonproprietary name, while in the US nomenclature is still unclear. The EMA allows the use of reference products outside of the European Union, while the FDA requires the reference product to be approved through the 351(a) pathway.

Biosimilars have been used in Europe since 2006. In 2004, the European Commission (EC) passed legislation creating a biosimilars approval pathway. In 2006 EMA approved Omnitrope® (somatropin- Sandoz), its first biosimilar product. To date, there have been 17 biosimilars authorized by the EMA. There are six unique chemicals that have been approved through the biosimilars pathway: epoetin alfa, follitropin alfa, filgrastim, infliximab, somatropin, epoetin zeta. The EMA was the first to implement a framework for authorizing biosimilars. Guidelines require comparing the biosimilar to the reference biologic based on quality, safety and efficacy.

The FDA and EMA are a part of a Biosimilars Cluster, started June 2011. The group was founded to facilitate the global development of biosimilars and share emerging scientific and regulatory issues. Collaboration may allow the use of reference products from either region with proper scientific data in the future.

Pending Issues

**Nomenclature:** The FDA is in the process of developing guidance due to a lack of consensus among stakeholders. Arguments have been made for biosimilars to have unique non-proprietary names for distinctive pharmacovigilance and safety profiles. However, arguments have also been made that non-proprietary names are unnecessary as a biosimilar’s national drug code, manufacturer name and lot number should be sufficient to identify differing products.

**Litigation:** The BPCIA indicates that biosimilar sponsors must share proprietary intellectual property such as details of manufacturing processes with the reference drug’s manufacturer. Patent disputes may prevent access to biosimilars.

**State Laws:** At this time, seven states have passed laws outlining requirements for pharmacists to substitute biosimilars for the reference product. All states but one (Florida), require that the prescribing physician is notified of the substitution. Differences in state legislation may impact access to biosimilars.

**Indication Extrapolation:** The FDA indicated that data extrapolation could be acceptable if data were derived from clinical study sufficient to demonstrate safety, purity and potency in an appropriate condition of use. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition, creating a costly process.

Express Scripts’ Stance

Express Scripts supports the development of biosimilars as these products will help mitigate growing biologic drug spend. Express Scripts’ external Pharmacy and Therapeutics (P&T) committee will review biosimilars once they reach the market, and clinically-appropriate formulary management will be implemented to help manage biologic drug spend.

Biosimilar Resources

2. FDA Biosimilars: [http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm](http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/default.htm)
**Biosimilars**  
**Frequently Asked Questions**

Q: **What is a biologic product?**  
A: A biologic is a complex molecule used for a variety of health conditions, derived from human or animal materials. Biologics are usually larger and more complex than chemically derived small molecule prescription medications.

Q: **What is a biosimilar?**  
A: A biosimilar is a biological product that is highly similar to a reference biologic and does not contain any clinically meaningful distinctions from the approved reference product in terms of the safety, purity and potency.

Q: **Are all biosimilars interchangeable with their reference products?**  
A: No. The 351(k) approval pathway requires a two step process for interchangeability to be established. Step 1, a non-interchangeable biosimilar product must be approved. Step 2, the manufacturer may conduct additional clinical trials to attempt to gain interchangeability with the reference product.

Q: **Are biosimilars generics?**  
A: No. The word “generic” applies only to small molecule drugs that are bioequivalent (the same) as an already approved small molecule medication under the FD&C Act. Biologic drugs are made from living organisms, thus no two batches will be exactly the same.

Q: **When do we expect to see the first biosimilar approved in the US?**  
A: It is expected that the FDA will rule on the approval of Sandoz’s biosimilar to Neupogen® (filgrastim – Amgen) in approximately eight months (Mar. 24, 2015).

Q: **Are the US and EMA approval pathways the same?**  
A: No. Approval differs in terms of use of foreign reference products, extrapolation of indications, clinical testing, interchangeability and naming guidance.

Q: **Why did Europe approve biosimilars first?**  
A: The EMA established a process to approve biosimilars in 2006 while the FDA did not have authority from Congress until 2010. Furthermore, reference biologics have longer patent protection in the US than Europe.

Q: **Which brand biologics are expected to see competition first?**  
A: The following are examples of biologics that are expected to come off patent protection and experience biosimilar competition within the next five years: Avastin® (bevacizumab), Epogen®/Procrit® (epoetin alfa), Fabrazyme® (agalsidase beta), Herceptin® (trastuzumab), Humira® (adalimumab), Neulasta® (pegfilgrastim), Neupogen® (filgrastim), Remicade® (infliximab) and Rituxan® (rituximab).

Q: **Why care about biosimilar approval?**  
A: Biosimilars have the potential to enhance competition, lead to better patient access and lower overall healthcare costs.

Q: **Where can I find more FAQs?**  
A: The FDA provides FAQs for health professionals, consumers, and industry sponsors.