Integrated Health Systems
Outcomes Coalition
AmerisourceBergen

Biosimilars:
Key Considerations

Executive Summary

As biosimilars launch, they are shaping the treatment landscape. These new options are also creating new opportunities for health system pharmacy leaders to expand their influence on patient outcomes and the total cost of care. Pharmacy teams who understand the requirements for biosimilar approval, as well as the key components for biosimliars, will be prepared to guide their health system on how to evaluate biosimilars for formulary inclusion. This white paper outlines those key components and provides specific questions that will facilitate the health system pharmacy team's partnership with the P&T Committee. Pharmacy teams will find our actionable comparison tool particularly helpful when discussing similarities between reference products and associated biosimilars with physician stakeholders.

Background

In March 2010, President Obama signed the *Patient Protection and Affordable Care Act (ACA)*, which included the development of a new approval pathway for biosimilar medicines, called the *Biologics Price Competition and Innovation Act (BPCIA). BPCIA* is an abbreviated licensure pathway for biologic products, referred to as biosimilars, that are demonstrated to be "highly similar" to the FDA-approved reference products. The purpose of the pathway is to improve access to biologic medicines and lower healthcare costs via improved competition. While approval pathways for generic products have existed for more than three decades before *ACA*, there was no pathway to bring highly similar copies of biologics to the market.

The United States has approved 11 biosimilars, but only three products have launched into the market. The others remain unlaunched as they are in various stages of litigation with the makers of the reference products. By contrast, the European Union established an approval pathway for biosimilars in 2006 and now has more than 40 approved and marketed biosimilars with more than 15 in various stages of approval.[1] Given that the EU approval pathway was established earlier than the U.S. pathway, the breadth of patient experience and safety data with biosimilars is significant. To date, the EU has more than 700 million patient days of experience with biosimilars with no significant differences in safety or efficacy identified.[2]

Requirements for Biosimilar Approval

The FDA regulates biologic products used to treat a variety of chronic and acute diseases, including immunology, oncology and vaccines. Biologics are generally very large, complex molecules and are typically produced in a living system. The nature of biologic products is complex, and since the manufacturing process produces batch-to-batch variation, a dynamic not seen in small molecule drugs, a new approval approach and pathway was warranted.

Since biologics are not chemically synthesized, there is no way to produce identical copies; not even the reference product is an exact copy of itself. As such, the FDA has built the approval pathway for biosimilars to be based on being "highly similar." According to the FDA, to be approved as a biosimilar, a manufacturer must demonstrate similarity through extensive analytics to characterize both the reference and biosimilar products. The majority of evidence requirements by the FDA lie within the analytical portion of the pathway. There are additional requirements including animal studies and a clinical study in the most sensitive population as determined by the FDA. These two sets of data comprise the "totality of evidence" approach, which is how the FDA ultimately determines approval for a biosimilar product.[3]

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As stakeholders—including manufacturers, payers, health systems, physicians and patients—seek to evaluate how biosimilars can be utilized, it is critical to understand the **key components of biosimilars**.

1. **Indication Extrapolation**

   Given that the approval pathway for biosimilars generally requires only one clinical study, indication extrapolation is a key component of the pathway. According to the FDA, if the totality of evidence for the biosimilar supports the demonstration of biosimilarity in one indication, then it can be scientifically justified that approval to other indications is warranted without clinical study. The FDA works closely with the biosimilar manufacturer during the product development process to assess what data are required to support extrapolation.

   While extrapolation answers the scientific question of indications, the patent question is considerably more complex. Orphan and pediatric patents, for example, carry different rules of exclusivity; therefore, biosimilars may not have all the reference product indications as a result of the patent landscape, not the FDA approval process.

2. **Totality of Evidence**

   As outlined above, the totality of evidence approach takes into account analytical, animal and clinical studies to develop the full body of evidence needed for biosimilar approval. While biosimilar manufacturers may opt to do additional clinical studies to further support the clinical value of their product, the pathway takes into account more analytical and animal data rather than clinical data. As stakeholders evaluate biosimilars for utilization, this is a critical understanding as the clinical evidence is the smallest component of data and is unlikely to show differences in safety or efficacy. If differences did occur that were meaningful, the biosimilar would not get approved by the FDA.

3. **Interchangeability**

   The designation of interchangeability for a biosimilar can be sought by a manufacturer with the addition of different data. The crux of interchangeability is that the biosimilar product is expected to produce the same clinical result as the reference product in any given patient. This is proven through additional data submitted to the FDA, including data from a clinical study focused on switching a patient between the reference and biosimilar product. When awarded, an interchangeable product may be substituted for the reference product without the involvement of the physician (subject to requirements outlined by state pharmacy laws). There have been no biosimilars awarded interchangeability as of March 2018, and only one biosimilar manufacturer has publicly stated they are undergoing a clinical study to support an interchangeability designation.

4. Post-Marketing Surveillance

The FDA has not set forth biosimilar-specific post-marketing surveillance requirements. Any requirements for biosimilars will be consistent with those set forth by the FDA for the reference product.

There are efforts outside the FDA to develop an ample amount of post-marketing data of biosimilars within the U.S. The most evolved is the Biologic and Biosimilars Collective Intelligence Consortium (BBCIC).[4] The BBCIC was established in 2015 to address anticipated stakeholder needs for post-marketing evidence generation for novel biologics and their biosimilar counterparts. The BBCIC is a non-profit initiative that will monitor both the novel biologic and biosimilars for efficacy and safety, and its results will be utilized to build the confidence of both patients and providers.

Considerations for Formulary Inclusion

As more biosimilars are FDA-approved, P&T Committees should develop a process to evaluate their utility as an addition to or replacement of the reference product. This assessment should incorporate many different factors including:

Efficacy and safety assessments

Manufacturer supply and hospital operational considerations

Economic impact based on cost and payer policies

Although it is standard for P&T Committees to assess safety and efficacy data for formulary reviews, there are unique considerations for evaluating biosimilar data. FDA guidance on review of biosimilar data states that clinical studies of biosimilars should include assessment of immunogenicity and pharmacokinetics/pharmacodynamics, and should be adequately designed "to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed."[3]

Because of the abbreviated nature of the biosimilar approval pathway and the greater reliance on analytical characterization, fewer clinical studies are typically available than would be for branded products. Even with limited data, it is expected that the P&T Committee approach to evaluating biosimilars should be completed with similar detail and thoroughness as conventional medications or branded biologics.[5]

Key components for consideration when reviewing biosimilars for formulary inclusion are outlined below:

Regulatory status

- Is the biosimilar FDA approved for the same indication(s) as reference product? If not, is the difference based on clinical studies or due to regulatory or patent exclusivity?

Clinical efficacy

- What clinical data are available? Are there additional data beyond that which is FDA-required for approval?
- Is the medical staff comfortable with using the biosimilar in indications for which it was extrapolated from the reference product without being studied for those indications?
- Are there any data available assessing multiple switches between the biosimilar and reference product (e.g., an interchangeability or bridge study)?
- Are there international studies with relevant clinical data available for review?
- Based on available data, are the P&T Committee and medical staff comfortable implementing a therapeutic equivalence protocol for the biosimilar? If so, will patients taking the reference product at home be included in the protocol and how will they be managed?

Pharmaceutics

- Are there any clinically meaningful differences in formulation or excipients of the biosimilar versus the reference product?
- Are there any clinically meaningful differences in drug or lab compatibility between the biosimilar and the reference product?

Biosimilar availability

- Does the manufacturer have experience in manufacturing biologics and/or biosimilars?
- Does the manufacturer have a history of drug shortages?
- Does the manufacturer have a process to guarantee a reliable supply of the biosimilar?

Operational considerations

- Are there any differences in storage, handling or preparation between the biosimilar and reference product?
- Are there any differences in commercially available dosage sizes or strengths between the biosimilar and reference product?
- How do you handle multiple biosimilars for the same product?
- If stocking the reference product and biosimilar, how will the electronic medical record be differentiated?
- What impact will that decision have on order set maintenance?

Economic considerations

- Are patient assistant programs available and similar to what is available for the reference product? If not, what is budget impact if added to the formulary?
- Are there any differences between the biosimilar and reference product with respect to the 340B Drug Pricing Program?
- Are there any differences between the biosimilar and reference product with respect to ease of access to the product based on payer requirements for preauthorization or limited distribution networks?[6]

Conclusion

Biosimilars represent a new class of drugs and face even more challenges than generics did years ago. However, there are many considerations to including a biosimilar on formulary and ensuring provider comfort in prescribing these medications. Affordability will be an important factor for patients as they consider treatment options; therefore, the financial impact should also be evaluated by providers and payers. Physician familiarity with and confidence in using biosimilars is critical to a successful formulary implementation. To that end, the biosimilar comparison tool on page seven can be used to facilitate discussion with physician stakeholders and emphasize the similarities between reference products and associated biosimilars.

References

[1] Adrian Van de Hoven, *Biosimilar Medicines for Europe*, presented to the Association for Accessible Medicines Annual Biosimilar Meeting, September 2017

[2] European Medicines Agency – European Commision, *Biosimilars in the EU – Information Guide for healthcare professionals*, April 2017

[3] FDA, *Biosimilar Development, Review, and Approval*, October 23, 2017, accessed February 2018 at fda.gov

[4] BBCIC, *Biologics and Biosimilars Collective Intelligence Consortium*, accessed February 2018 at bbcic.org

[5] C. Ventola, *Evaluation of biosimilars for formulary inclusion: factors for consideration by P&T committees*, Pharmacy and Therapeutics, Oct. 2015; 40(10):680-9

[6] N.Griffith, A. McBride, J. Stevenson, et al., *Formulary selection criteria for biosimilars: considerations for US health-system pharmacists.* Hospital Pharmacy. Oct. 2014;49(9):813-25

Biosimilar Comparison to Reference Product Tool

Parameter	Reference Product	Biosimilar for Comparison
Domain 1: Regulatory Status		
What are the FDA-labeled indications for the reference product and biosimilar product?		
Domain 2: Clinical Data		
For which disease states have the reference product and biosimilar product been studied?		
What is the FDA approved dosing, by indication, for each product?		
Domain 3: Safety Data		
What are the most commonly reported adverse effects and associated frequencies?		
What are the most severe reported adverse effects and associated frequencies?		
How common are serious immunogenic reactions or anti-drug antibody development during use of the biosimilar or reference product?		
Domain 4: Pharmaceutics		
Are there any differences in commercially available dosage sizes or strengths between the biosimilar and reference product? If so, include.		
Are there any clinically significant differences in formulation or excipients of the biosimilar versus the reference product? If so, include.		

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About IHOC

The Integrated Health Systems Outcomes Coalition (IHOC) is committed to supporting and improving the access, value and delivery of quality care for patients with specialty diseases through a unique partnership between health systems, manufacturers, payers and supply chain partners. IHOC, an independent LLC created by AmerisourceBergen, believes actionable data may help all involved stakeholders demonstrate the value of specialty pharmaceuticals and the coordination of patient care services provided in health system settings. Visit **ihocnetwork.com** to learn more.