REPORT

Biosimilars: Biologics That Meet Patients' Needs and Healthcare Economics

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ABSTRACT

Biologics have revolutionized medical care, yet uniform access to these effective medicines remains difficult due to the increasing costs of healthcare. As patent exclusivity on the early biologics wanes, regulatory and legal systems are adapting to bring competition to the field in the form of biosimilars. Biosimilars are biologics that offer the same clinical benefit in one or more of the same indications as the reference biologic drug and bring competition to the biologics space. Legislation creating a pathway resulting in the first US approvals of biosimilars has been in place since 2010, but the regulatory methodology and science of evaluating the sameness of two biologics has been in use for decades. The demonstration of biosimilarity is based on the "totality of the evidence" concept, in which all structural, functional, nonclinical, and clinical data for a biosimilar product are evaluated to show high similarity to the reference product. Clinical trials for biosimilars, therefore, are designed to confirm similarity, or discover clinically relevant differences between the reference product and the biosimilar, should differences exist. It is hoped that competition from biosimilars will drive biologic innovation and increase patient access to biologics.

***Am J Manag Care*. 2016;22:S439-S442**

For author information and disclosures, see end of text.

Biologics have revolutionized medical care due to their targeted efficacy, speed of onset, and tolerability.[1] A number of biologics are currently licensed for the treatment of various autoimmune diseases and cancer, including tumor necrosis factor-alpha (TNF) inhibitors and agents targeting specific cancers or oncologic pathways, such as trastuzumab, rituximab, and bevacizumab.[2] These drugs are a significant part of healthcare system spending. By 2020, global biologic sales are estimated to exceed $390 billion.[3] However, the converging opportunities of patent expirations on these medicines, newly implemented regulatory pathways, and state-of-the-art manufacturing and analytical capabilities are enabling competitors to produce and bring to market their own versions of these biologics.

Biologic drugs are developed using sophisticated recombinant DNA technology, wherein a gene is inserted into a host cell for manufacturing of a specific protein. The host cell uses its own metabolic machinery to manufacture the desired protein or glycoprotein, which is then isolated for human use. Using these biological systems, however, produces complex protein-based drugs that have variability from one molecule to the next, as found in nature.[4] The amino acid sequence is the same between molecules, but the chemical "ornaments," or post-translational modifications placed on the protein by the cell can vary within the same and between batches of drug. This variability is commonly seen in nature and is tolerated by the human body if it is kept within certain bounds. For example, we tolerate variations in erythropoietin (red blood cell stimulator) that are produced in our own body with differing glycosylation patterns that are called isoforms. Such biologic tolerance has made the manufacturing and human use of complex biologics feasible in many diseases.

However, despite their clinical benefit, many biologic therapies are costly, and broad patient access has not been possible. Fortunately, many of the initially approved biologic drugs have reached, or are close to reaching, the time of patent expiry. This has led to an increasing focus by legislators, regulatory authorities, and the pharmaceutical industry to allow manufacturers other than the originator to develop and manufacture their

own versions of these biologics, which have been described as "follow-on biologics" or "biosimilars." In the United States and the European Union, biosimilar is a regulatory term reserved to describe products that are approved following a stringent regulatory review in which a complete data package is evaluated consisting of far more analytical but often less clinical data than a traditional Biologics Licensing Application.[5] Similarly, "subsequent entry biologic" is the term used for the same category by Canadian authorities.[6]

Unfortunately, neither of the terms are ideal, because they can communicate a perception that the newly approved versions are "different" in function from the original drug, when, in fact, biosimilars are biologics that are essentially the same as an already licensed originator (reference) product.[7] The biosimilar sponsor develops its own manufacturing process for both the drug substance (making the molecule) and the drug product (putting the molecule in a formulation) independently from the company that developed the reference product because that company's manufacturing processes generally are not known or in the public domain. The data supporting the "sameness" of the biosimilar to the reference product must be generated entirely by the biosimilar manufacturer.

Biosimilar Development

The development and approval of a biosimilar requires a paradigm shift in the approach to biologic development. All biologics possess intrinsic variability in molecular features, or quality attributes, so it is not possible to demonstrate that each batch of reference product is chemically identical. For the same reason, it is not possible to demonstrate that a reference biologic and a biosimilar are identical. Regulatory science and the evolution of analytical capabilities enable the evaluation of the reference product and the proposed biosimilar product in many dimensions, including structure, function, and clinical outcomes. Such an approach is based on the "totality of the evidence" concept, whereby the orthogonal sets of physicochemical, functional, nonclinical, and clinical data of a biosimilar product are used to demonstrate that the proposed drug is essentially the same as the reference product.[8] This approach has been used for more than two decades to evaluate differences in molecular attributes of the reference product between batches and when manufacturing changes are made to conclude that the reference product is "highly similar" to itself over time.[9]

The development of biosimilars is based on a stepwise approach consisting of several stages.[4,10] The first step involves understanding the normal variability of the reference product as seen over time.[11] This observed variability in the reference product defines goalposts or targets for product attributes of the proposed biosimilar.[12] Multiple batches of the reference product are characterized to understand molecular structures, which are called "quality attributes," and include protein structure, post-translational modifications, and bioactivity. Variability of these quality attributes in the reference product from batch to batch, and over time, defines the boundaries of variability that are then used for biosimilar development. Relatively large patient populations have been exposed to the reference product containing these variations in molecular structure or quality attributes, demonstrating that humans tolerate such variability without altering the safety or efficacy of the biologic product.[11]

The second stage involves target-directed development of the biosimilar, with the understanding of the variability of the molecular structure and function that the reference product has displayed over time. This comparative analytical approach results in a drug substance that is highly similar to the reference product. Throughout the target-directed development phase, a comprehensive analytical assessment is performed using state-of-the-art methods to compare the proposed biosimilar with the reference product at physicochemical and functional levels. This serves as the foundation of the overall comparability exercise.[13]

The final stage of biosimilar development involves confirmation of similarity using functional assessments in preclinical models and human studies. Human pharmacokinetic (PK) and pharmacodynamics (PD) studies are typically conducted in healthy volunteers. Equivalent PK and PD profiles between the biosimilar and the reference product confirm prior analytical and functional data, demonstrating that the biosimilar is essentially the same as the reference product. The degree of structural similarity and results from the PK and PD studies are used to support the design of a confirmatory clinical safety and efficacy study in patients. The goal of a clinical study in patients is to confirm similarity. Therefore, clinical studies for biosimilar development may have unique designs that are different from studies originally used to demonstrate the safety and efficacy of the reference product.[14]

Biosimilar clinical trial designs are unique in that they attempt to investigate and identify small differences that would not be evident using traditional end points. For example, multiple anti-TNF biologics produce overlapping efficacy signals using the traditional ACR20 primary end point in rheumatoid arthritis at 24 months, even though these molecules are structurally quite different. Therefore, using the traditional end point approach would not be an effective way to differentiate between a reference product and its proposed biosimilar, even with substantial molecular differences. Another approach would be to analyze disease activity severity several times early in the course of the trial; although this would be a more sensitive approach to evaluate differences in the molecules, it is not a traditional approach used in clinical trials.

Other unique features of biosimilar clinical trials are discussed elsewhere,[14] such as using an indication not within the label of the reference product, using healthy volunteers in PD studies, and

using doses lower than those approved for the reference product. Although such trial designs may seem perplexing or inappropriate to those unfamiliar with the biosimilar concept, the goal of the confirmatory clinical studies in biosimilar development is to use the clinical indication, primary end point, and length of study to maximize the likelihood of identifying any differences between the reference product and the biosimilar should such differences exist.

The ultimate goal is to provide data to demonstrate that the biosimilar is "essentially the same" as the reference product, with no clinically meaningful differences. Therefore, the goal is not to repeat the safety and efficacy study designs originally performed by the reference product sponsor. The goal is to provide a data package, often referred to as the totality of evidence, demonstrating the sameness of the biosimilar to the reference product from an analytical, functional, and clinical perspective.

Moreover, the confirmatory clinical trial allows for the direct comparison of immunogenicity produced by both the reference product and the proposed biosimilar. For that reason, it is optimal, if possible, to compare the biologic products using monotherapy without co-medications. For example, the treatment of patients who have rheumatoid arthritis with etanercept is generally combined with methotrexate, which can suppress the immune response to the biologic drug. Using a different indication that does not use a co-medication, such as psoriasis, would be more sensitive in identifying a difference in immunogenicity, if one existed. If the biosimilar is proven to be essentially the same biologic substance as the reference product, as per regulatory requirements,[15] then healthcare providers and patients can expect the same clinical outcomes with the biosimilar as the reference product in the same indications.[16-18] Rather than undertaking clinical trials of the biosimilar in every indication of the reference product, the totality of evidence demonstrating that the active biologic drugs are essentially the same is used to justify that it is appropriate to use the biosimilar in all indications of the reference product (the same product will produce the same effect).

This extrapolation justifies why only a single confirmatory study to evaluate the efficacy and safety of the biosimilar is conducted to address any residual uncertainty that the biosimilar is essentially the same as the reference product. It is important to note, however, that extrapolation of indications from the reference to the biosimilar is not automatically granted and is evaluated by regulators on a case-by-case basis, taking into account the mechanism of action and each specific clinical indication.[19]

Conclusion

The adoption of regulatory pathways to evaluate biosimilars has led to the approval of a number of biosimilars globally. The first biosimilar (Omnitrope® [somatropin], Sandoz GmBH) was approved by the European Medicines Agency in 2006.[20] A decade later, there are 22 biosimilar medicines available in Europe, comprising hormones, epoetins, granulocyte colony-stimulating factors, insulins, and TNF inhibitors.[10,21] In 2015, a biosimilar filgrastim (Zarxio®; Sandoz Inc) became the first biosimilar approved by the FDA,[22] paving the way for the approval of a biosimilar infliximab (Inflectra™; Celltrion) in 2016. In all instances, the manufacturer was able to demonstrate to regulatory authorities that the proposed biosimilar was as similar to the reference product as the reference product was to itself over its lifetime.

It is estimated that almost 50 biosimilars are currently in development, which will have a potentially significant impact on the competitive marketplace.[3] It is hoped that the availability of biosimilars will promote competition, drive biologic innovation, and increase patient access to more biologic medicines.[23] Ultimately, with increasing treatment options, healthcare providers will have the ability to deliver a more nuanced and targeted treatment plan to their patients.

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Funding source: This supplement was sponsored by Sandoz Inc.

Author disclosures: Dr McKay reports employment at Sandoz and expert testimony for state legislation on biosimilars. Dr Yoon reports employment at Sandoz, expert testimony for state legislation, biosimilar conference attendance and conference speaking, and stock ownership in Novartis.

Authorship information: Concept and design (MM, JM, WY); drafting of the manuscript (MM, JM, WY); critical revision of the manuscript for important intellectual content (JM, WY); administrative, technical, or logistic support (MM, WY); and supervision (MM, WY).

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