The Era of Therapeutic Biosimilars Has Arrived: What You Need to Know

Presented by Andrew D. Zelenetz, MD, PhD

ABSTRACT

Although complex, biologic agents are key components of modern therapy in multiple disciplines, particularly oncology. However, despite the fact that biosimilars (eg, filgrastim-sndz, bevacizumab-awwb, trastuzumab-dkst, rituximab-abbs) have been approved in the United States, many clinicians are poorly informed about their unique pathway for approval. At the NCCN 2019 Annual Congress: Hematologic Malignancies, Dr. Andrew D. Zelenetz, Memorial Sloan Kettering Cancer Center, outlined important issues regarding the use of biosimilars, including extrapolation, interchangeability, and naming.

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Biosimilars From a Clinician Perspective

Since the approval of filgrastim-sndz in 2015, the list of approved biosimilars has grown to include those for use in supportive care and, subsequently, those used for therapy in both oncology and nononcology settings (Figure 1). Nevertheless, confusion about this topic abounds, particularly with respect to the unique pathway for approval. At the NCCN 2019 Annual Congress: Hematologic Malignancies, Andrew D. Zelenetz, MD, PhD, Medical Director, Quality Informatics, Memorial Sloan Kettering Cancer Center, discussed regulatory criteria for approval of biosimilars, including requirements for extrapolation and interchangeability.

As Dr. Zelenetz explained, biosimilars are products that have been shown to be highly similar to the reference product in appropriate comparative, head-to-head, non-clinical and clinical studies. The FDA defines a biosimilar as a “biological product that is highly similar to a US-licensed reference biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product.”¹

The Biologics Price Competition and Innovation Act (BPCI Act) of 2009 created an abbreviated licensure pathway for biologic products that are shown to be biosimilar to or interchangeable with an FDA-approved biologic product, said Dr. Zelenetz, and the FDA has subsequently issued a series of biosimilars guidance documents providing information regarding development.² NCCN is also developing a policy regarding inclusion of biosimilars in the NCCN Guidelines, which is pending final approval, he reported.

According to Dr. Zelenetz, the bulk of biosimilarity determination is conducted in preclinical studies, although the rulings and guidance require evaluation in an appropriately sensitive clinical indication. Intended copies of the licensed biologic products that have not undergone the exhaustive comparative analysis of a biosimilar are called “me-too biologics,” whereas those that have been structurally and/or functionally altered to achieve an improved or different clinical performance are known as “biobetters.”³ The latter must go through the full development and approval process in a standard 351(a) application.

Biosimilars Are Not Generics

Although drugs such as atorvastatin have a very defined chemical structure, Dr. Zelenetz stated, biologics are inherently large, complex products that can be affected by changes in any step of production. Changes in process could include scale, purification, packaging, and sourcing of media and other reagents. Although lot-to-lot variation in analytic results is expected—there is lot-to-lot variation even among the originators, Dr. Zelenetz said—they must fall into pre-defined specifications to be acceptable. If preclinical analytics show a change in the product, a clinical trial may be necessary to demonstrate an impact on clinical efficacy.

Preclinical assessment involves an exhaustive clinical evaluation to establish that there are no clinically meaningful differences (“highly similar” or “highly similar with fingerprint-like similarity”) between the biosimilar and the reference biologic product. All of the physiochemical properties (eg, primary sequence, peptide mapping, higher order structures, and glycosylation status) must be identical or nearly identical. “Interestingly,

Supportive Care	
Drug Name	Approval Date
Udenyca (pegfilgrastim-cbqv)	November 2018
Nivestym (filgrastim-aafi)	July 2018
Fulphila (pegfilgrastim-jmdb)	June 2018
Retacrit (epoetin alfa-epbx)	May 2018
Zarxio (Filgrastim-sndz)	March 2015
Therapeutic: Oncology	
Drug Name	Approval Date
Ruxience (rituximab-pvvr)	July 2019
Zirabev (bevacizumab-bvzr)	June 2019
Kanjinti (trastuzumab-anns)	June 2019
Trazimera (trastuzumab-qyyp)	March 2019
Ontruzant (trastuzumab-dttb)	January 2019
Herzuma (trastuzumab-pkrb)	December 2018
Truxima (rituximab-abbs)	November 2018
Ogivri (trastuzumab-dkst)	December 2017
Mvasi (Bevacizumab-awwb)	September 2017
Therapeutic: Non-Oncology	
Drug Name	Approval Date
Hadlima (adalimumab-bwwd)	July 2019
Eticovo (etanercept-ykro)	April 2019
Truxima (rituximab-abbs)	November 2018
Hyrimoz (adalimumab-adaz)	October 2018
Ixifi (infliximab-qbtx)	December 2017
Cyltezo (Adalimumab-adbm)	August 2017
Renflexis (Infliximab-abda)	May 2017
Amjevita (Adalimumab-atto)	September 2016
Erelzi (Etanercept-szzs)	August 2016
Inflectra (Infliximab-dyyb)	April 2016

Figure 1. FDA-approved biosimilars as of July 2019.

the impurities must be the same,” said Dr. Zelenetz, who noted that functional assays are then required to show that the biosimilar functions in the same way.

Importantly, reported Dr. Zelenetz, despite the high level of analytic characterization required, the clinical efficacy and safety of the biologic molecule have already been demonstrated by the innovator. The biosimilar sponsor only requires evidence that the candidate biosimilar has no clinically meaningful differences from the reference product.

“In other words, there’s no need to recreate the wheel and replicate unnecessary clinical trials,” said Dr. Zelenetz. “Otherwise, there’d be no advantage to creating a biosimilar.”

Because these are large molecules, immunogenicity is a major concern. According to Dr. Zelenetz, an exhaustive evaluation of immunogenicity is important along with the commitment—even after drug approval—to maintain a registry and monitor for immunogenicity of biologic molecules.

Extrapolation: Current Use and Role in Biosimilar Development

Extrapolation—expansion of use of an approved agent from one indication to another based on clinical and safety data—is an essential element in the development of biosimilars (Figure 2). According to Dr. Zelenetz, scientific justification for extrapolation should consider the mechanism of action in each condition; pharmacokinetics, pharmacodynamics (if important for mechanism of action), and biodistribution of product in different patient populations; immunogenicity of the product in different patient populations; differences in expected toxicities for each condition and patient population; and “any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.”^{2,4}

“If you have a biologic that meets all of those requirements, you should be able to extrapolate from one indication to another, which potentially provides substantial savings in drug development,” said Dr. Zelenetz.

Are Studies in Rheumatoid Arthritis Adequate for Extrapolation to B-Cell Non-Hodgkin’s Lymphoma?

As Dr. Zelenetz explained, an attempt to extrapolate the biosimilar rituximab-abbs, approved for rheumatoid arthritis (RA), to lymphoma demonstrates the high burden of proof required. Although the mechanism of action in both lymphoma and RA is antibody-dependent cell-mediated cytotoxicity, the target in RA is normal B-cells, where in B-cell non-Hodgkin’s lymphoma (NHL), it is malignant B-cells. Rituximab pharmacokinetics also differs between lymphoma and RA, which supports different dosing approaches. Finally, said Dr. Zelenetz, immunogenicity is vastly different: in RA, anti-CD20 antibodies develop in 15% to 17% of patients, whereas in lymphoma, the risk is very low (<1%).

“Based on these differences, extrapolation from RA to B-cell NHL does not appear to meet the framework for extrapolation, and lymphoma-specific studies are most appropriate,” he concluded.

A study of biosimilar rituximab versus innovator product in patients with untreated advanced-stage follicular lymphoma showed identical pharmacokinetics and pharmacodynamics (although different from RA), and the overall response rate, although slightly higher for the biosimilar product, met prespecified margins.⁵ Progression

Figure 2. Framework for extrapolation of biosimilars. Data from FDA² and Weise et al.⁴

events and adverse events were also nearly identical, and no meaningful difference was seen in immunogenicity in both RA and follicular lymphoma. Based on these data, the biosimilar rituximab (rituximab-abbs) was approved for treatment of follicular lymphoma. However, full extrapolation to other lymphoma indications was denied.

“In my opinion, there is no reason not to extrapolate the findings,” said Dr. Zelenetz. “I suspect the restricted approval was due to the limited sample size of the study. The FDA acted a little bit conservatively here.”

As Dr. Zelenetz explained, interchangeability demands an even higher standard than biosimilarity. The designation of interchangeability requires switching between reference product and biosimilar with no clinical consequences. Although the FDA has provided guidance regarding how a study must be conducted, said Dr. Zelenetz, no drug has been approved as interchangeable yet.

Naming of Biosimilars

The FDA has decided to use suffixes containing 4 random letters (approved by both the 351(k) biosimilar pathway as well as the 351(a) NDA pathway) for all biologic products, including all innovator molecules.⁶ This process of having a common root with a distinguishing suffix helps distinguish a biosimilar from the originator product and allows for tracking of pharmacologic events should they arise, Dr. Zelenetz concluded.

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