

# New Biosimilar Approvals for Myeloid Growth Factors and Anemia

Presented by Gary H. Lyman, MD, MPH, FASCO, FACP, FRCP

## ABSTRACT

Biosimilars are here to stay, but whether they will enjoy widespread uptake remains to be seen. The FDA sets a high bar for approval of biosimilar products, yet many clinicians remain skeptical about the efficacy and safety of these agents. Favorable experience with >30 biosimilars in Europe provides some reassurance that these agents are safe and effective and can be substituted for the reference product.

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**“The continued rapid rise** in healthcare costs is unsustainable and imposes a considerable financial burden on patients, potentially limiting access to effective cancer therapies. The median cost of launching new cancer therapies is now more than twice that of the median household budget in the United States. Although drugs are not the only driver of healthcare costs, the introduction of biosimilars for drugs known and trusted for many years is one possible solution,” explained Gary H. Lyman, MD, MPH, FASCO, FACP, FRCP, Senior Lead for Healthcare Quality and Policy, Hutchinson Institute for Cancer Outcomes Research, Fred Hutchinson Cancer Research Center, and Professor of Medicine, University of Washington School of Medicine. “As patents for cancer drugs expire, pharmaceutical companies are encouraged to develop highly similar agents. The profit motive for competing in this lucrative market cannot be overstated and runs into the billions of dollars,” he added.

Biologics currently represent approximately 20% of the global therapeutic market. More biologics are approved for use in the European Union (EU) than in the United States, and the EU has more than a decade of experience with biosimilars, providing reassurance regarding their safety and efficacy.

### What Is a Biosimilar?

According to the FDA, a biosimilar is “a biological product that is highly similar to a US-licensed reference biological product for which there are no clinically meaningful differences in safety, purity, or potency of the product.”<sup>1</sup>

“Biologics, including biosimilars, are complex molecules produced in living systems or organisms. They cannot be replicated chemically, and it is impossible to fully characterize the molecular composition of a biosimilar. They are unstable compounds sensitive to external

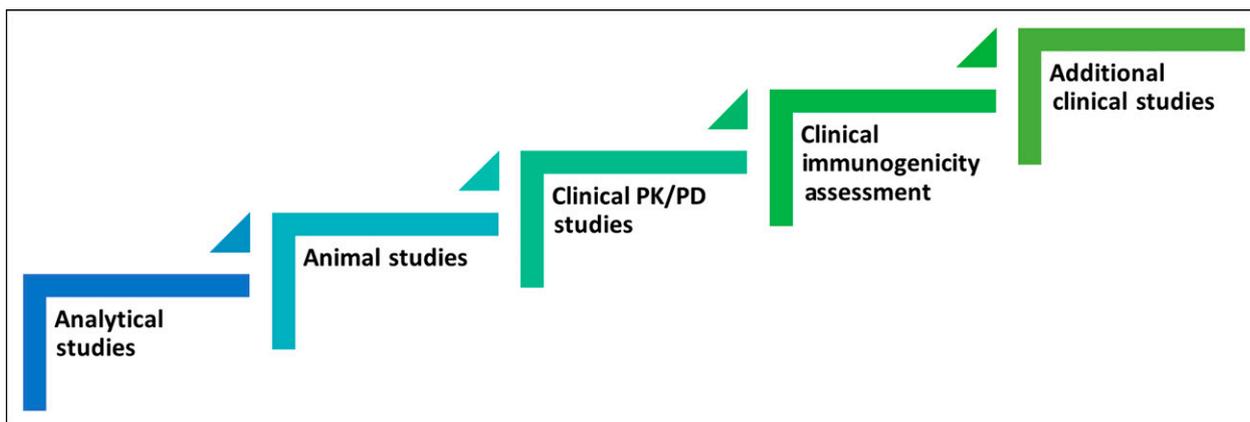
conditions, and are likely to be immunogenic,” Dr. Lyman explained. “It takes hundreds of millions of dollars to develop a biologic,” he added. “They are larger and more complex than chemically synthesized drugs.”

Not surprisingly, the FDA sets a high bar for the licensing pathway of a biosimilar, starting with analytical studies, followed by animal studies, clinical pharmacodynamic and pharmacokinetic studies, clinical immunogenicity assessment, and additional studies as needed (Figure 1). At each of these steps, the FDA evaluates the totality of evidence to determine whether further studies are required to eliminate residual uncertainty between the biosimilar and reference product. “A biosimilar should also not be more immunogenic than the reference product,” he explained.

### Biosimilar US Approvals

In March 2015, filgrastim-sndz was the first biosimilar to be approved in the United States, and it was granted approval for all the same indications as the reference product. Filgrastim-sndz has the same protein structure, mass, size, charge, and hydrophobicity as the reference product, and the same mechanism of action of binding to granulocyte colony-stimulating factor (G-CSF) receptors.<sup>2</sup> A phase III trial in 218 patients with breast cancer showed that the biosimilar filgrastim was equally effective as the reference product in the prevention of neutropenia in patients receiving myelosuppressive chemotherapy.<sup>3</sup> Filgrastim-sndz was subsequently approved for the treatment of neutropenia in patients with breast cancer.

Dr. Lyman explained that other studies, including retrospective studies, have confirmed the similar efficacy and safety of the biosimilar to the reference product. “Filgrastim-sndz met all FDA criteria for extrapolation to other indications for which the reference product was licensed. The mechanism of action for each condition was



**Figure 1.** Approval pathway for biosimilars in the United States: totality of evidence. At each step, the FDA evaluates totality of evidence to determine if further studies are required to eliminate residual uncertainty between the biosimilar and the reference biologic.

Data from US Department of Health and Human Services, Food and Drug Administration. Scientific considerations in demonstrating biosimilarity to a reference product. Available at: <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>. Published April 2015. Accessed April 10, 2019.

likely to be the same. The pharmacokinetic and bio-distribution were likely to be the same. Expected toxicities were likely to be the same, and so were any other factors,” he continued. Therefore, additional indications for the original reference product were extrapolated by the FDA to include treatment of neutropenia in patients who have undergone a bone marrow transplant, of nonmyeloid malignancies (eg, acute myeloid leukemia), of severe chronic neutropenia, and for progenitor cell mobilization or collection.

### Concerns About Biosimilars

Beyond data presented to the FDA, biosimilars are subject to variability and drift over time due to production at different sites and changes to the manufacturing processes after the initial approval. Furthermore, FDA or European Medical Association approval is required for changes in the manufacturing process.<sup>4</sup> “Manufacturers need to be vigilant for any changes in production and must always assume that such changes can result in clinically significant issues. It is important to note, however, that both originator biologics and biosimilars are subject to product variability and drift,” Dr. Lyman advised.

Immunogenicity is also a concern for all biologics, the consequences of which may include loss of efficacy, neutralizing antibodies, and general immune reactions. Comparative head-to-head studies are required to compare the immunogenicity of biosimilars and the reference product. Often, these studies are performed in healthy volunteers who are immunocompetent and thought to be most sensitive to such effects.

Another issue is whether biologics are potentially “interchangeable,” a designation that is based on higher standards from the FDA than those for the approval of the biosimilar alone. Interchangeability means that an approved biosimilar could be substituted for a

reference product without the intervention of the provider. Dr. Lyman noted that, “Interchangeability is a concern for the future. It doesn’t apply to biosimilars at the present time. No biosimilar in the United States currently has an interchangeable designation.”

“Nomenclature is important,” Dr. Lyman continued. The nomenclature of biosimilars in the United States includes the nonproprietary name of the reference product plus a suffix that is unique, devoid of meaning, nonproprietary, and has no legal barriers. Some examples of nomenclature for FDA-approved biologics are adalimumab-atto, etanercept-szszs, and infliximab-abbd.

Over the past decade, increasing numbers of patents for biologic therapies used in the treatment of cancer have expired. “Each one of these biologics represents an opportunity to generate billions in global spending if a biosimilar is developed,” he said.

Currently, 2 filgrastim biosimilars are available in the United States: filgrastim-sndz and filgrastim-aafi, both approved in 2018. Both biosimilars had phase III data available to support their approval. Additionally, 2 pegfilgrastim biosimilars are approved for use in the United States: pegfilgrastim-jmbd and, more recently, pegfilgrastim-cbqv. Other approved biosimilars include the erythropoietin-stimulating agent epoetin alfa-epbx and the monoclonal antibodies trastuzumab (with 4 biosimilar products with the suffixes -pkrb, -dttb, -dkst, and -qyvp), rituximab-abbs, and bevacizumab-awwb (Figure 2).

### Hematopoietic Growth Factors

The 2019 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Hematopoietic Growth Factors include appropriate risk assessment for febrile neutropenia following chemotherapy that is similar to other guidelines

Active Substance	Approval Date
<b>Granulocyte colony-stimulating factors</b>	
Pegfilgrastim-jmdb	June 2018
Pegfilgrastim-cbqv	November 2018
Filgrastim-aafi	July 2018
Filgrastim-sndz	March 2015
<b>Erythropoiesis-stimulating agents</b>	
Epoetin alfa-epbx	May 2018
<b>Monoclonal Antibodies</b>	
Rituximab-abbs	November 2018
Trastuzumab-pkrb	December 2018
Trastuzumab-dttb	January 2019
Trastuzumab-dkst	December 2017
Trastuzumab-qyyp	March 2019
Bevacizumab-awwb	September 2017

**Figure 2.** Biosimilars FDA-approved for use in oncology.

in different cancers. In high-risk patients (>20% risk of febrile neutropenia), use of G-CSF prophylaxis in this setting is a category 1 recommendation. For intermediate-risk patients (10%–20% risk), G-CSFs should be considered dependent on individual patient risk factors. “Intermediate-risk patients are always a challenge in this regard,” Dr. Lyman noted. In low-risk patients (<10% risk), routine use of G-CSFs is not recommended.

Based on the updated NCCN Guidelines for Hematopoietic Growth Factors, in addition to the originators, the 4 new biosimilars of G-CSF can be used. “After review of the available preclinical and clinical data, it’s been judged that they are safe and efficacious for the prevention of febrile neutropenia,” he stated. The NCCN Guidelines for Hematopoietic Growth Factors also include use of the biosimilar compound epoetin alfa-epbx for the treatment of chemotherapy-induced anemia in patients receiving chemotherapy or with chronic kidney disease.

### Remaining Concerns

Despite biosimilars passing the high bar for approval set by the FDA, many clinicians remain skeptical of their safety and efficacy, as well as reimbursement. Clinicians are also concerned that biosimilars will be “forced down their throats,” he commented.

“It will be important to provide additional evidence regarding their safety and efficacy” in order to diminish clinician skepticism, Dr. Lyman continued. It is important

that providers and professional organizations such as NCCN have access to the data submitted to FDA for regulatory approval, thus ensuring transparency of the data based on public presentation or publication in a peer-reviewed journal. Professional education will also be essential to promoting and expanding access to biosimilars.

“In the EU, there are currently >30 biosimilars approved for use. It is reassuring that so far none has been withdrawn or suspended. The European monitoring system has not found any relevant safety differences between biosimilars and reference products over the past 10 years,” he told the audience.

Additionally, ASCO published an education policy statement on biosimilars designed to improve understanding and provide further education about the development, regulation, safety, and value of these agents.<sup>5</sup> “[ASCO’s] conclusion is that biosimilars will play an important role in the future care of patients with cancer and will improve access to valuable medicines,” Dr. Lyman stated.

Currently, there are limited data on the early adoption of biosimilar hematopoietic growth factors in the United States. According to one estimate, filgrastim biosimilars now account for approximately 50% of the US filgrastim market.<sup>6</sup>

“Biosimilars are here to stay. They are already being incorporated into clinical practice. We all need to recognize that there must be a balance between how much data we require and what is practical from a development perspective. More data provide greater reassurance, but there may be a tipping point in terms of the costs of acquiring more data that handicaps the development of these agents. On the other hand, we need to require enough data so we have confidence in the safety and efficacy of biosimilars,” he commented.

Dr. Lyman’s advice to oncologists was to “Be vigilant and report anything unusual and unexpected as we increasingly incorporate these new agents into clinical practice.”

**Disclosures:** Dr. Lyman has disclosed that he has served as a consultant for Amgen Inc., Genomic Health, Inc., Halozyme, Inc., Mylan, Partners Healthcare, Pfizer Inc., Samsung Bioepis, and Spectrum Pharmaceuticals, Inc.

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