Biosimilars

Considerations for oncology nurses

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BACKGROUND: Biosimilars are developed to be highly similar to and treat the same conditions as licensed biologics. As they are approved and their use becomes more widespread, oncology nurses should be aware of their development and unique considerations.

OBJECTIVES: This article reviews properties of biosimilars; their regulation and approval process; the ways in which their quality, safety, and efficacy are evaluated; their postmarketing safety monitoring; and their significance to oncology nurses and oncology nursing.

METHODS: A search of PubMed and regulatory agency websites was conducted for references related to the development and use of biosimilars in oncology.

FINDINGS: Because biologics are large, structurally complex molecules, biosimilars cannot be considered generic equivalents to licensed biologic products. Consequently, regulatory approval for biosimilars is different from approval for small-molecule generics. Oncology nurses are in a unique position to educate themselves, other clinicians, and patients and their families about biosimilars to ensure accurate understanding, as well as optimal and safe use, of biosimilars.

KEYWORDS: biologics; biosimilars; oncology; postmarketing safety; clinical practice

DIGITAL OBJECT IDENTIFIER 10.1188/17.CJON.E54-E60

THE INTRODUCTION OF BIOLOGIC THERAPIES has revolutionized the treatment of patients with cancer and autoimmune inflammatory disorders. Biologics are drugs that are derived from a living organism or its products and are typically made by genetically engineering living systems, such as bacterial, yeast, animal, or plant cells. Biologic drugs are an essential part of cancer treatment, providing targeted therapy and supportive care. The biologics bevacizumab (Avastin®), epoetin alpha (Epogen®), infliximab (Remicade®), pegfilgrastim (Neulasta®), rituximab (Rituxan®), and trastuzumab (Herceptin®) are among the top 15 medications used in hospitals and clinics (Hoffman et al., 2013). Many patients cared for by oncology nurses will receive a biologic therapy at some point during their treatment.

Patents for several biologics have expired or will soon expire, fueling interest in and removing barriers to the development of highly similar versions of licensed biologics (also known as “reference” or “originator” products). Table 1 provides U.S. patent expiration dates for selected biologics. In contrast to small-molecule drugs, which are typically created through chemical synthesis, biologics are large, structurally complex proteins developed using living systems and often requiring development of cell lines specifically engineered to produce highly targeted molecules. Because biologics have inherent complexity and heterogeneity, making an identical copy of a biologic without the originator’s cell line and specific manufacturing conditions is not possible. Accordingly, “biosimilar” refers to a biologic product developed to be highly similar to and used to treat the same conditions as a licensed biologic. By providing additional treatment choices (Rompas et al., 2015), biosimilars may increase access to and expand use of biologic therapies, which may lead to better overall health outcomes and patient care. In addition, the introduction of biosimilars has the potential to deliver savings and increase efficiencies for healthcare systems, thereby freeing resources for other facets of health care.

Legislation enacted across the world allows for the approval and licensing of biosimilars (European Medicines Agency [EMA], 2014; Health Canada, 2016a; U.S. Food and Drug Administration [FDA], 2015b). As biosimilars are approved and their use becomes more widespread, oncology nurses should understand the unique development of and considerations for biosimilars. This article reviews key properties of biosimilars and how they differ from generic drugs; summarizes the regulation and approval of biosimilars; describes evaluation of biosimilar quality, safety, and efficacy; outlines postmarketing safety monitoring; and highlights the role that oncology nurses, who are often the first and most frequent point of contact for patients undergoing cancer treatment, play in the education of patients and their families about biosimilars.
**Complexity of Biosimilars**

Because biologics are large, structurally complex molecules, biosimilars cannot be considered generic equivalents to licensed or approved biologics. Differences exist between biosimilars and small-molecule generic drugs in their fundamental properties (e.g., structure, size, characterization) (see Figure 1), as well as their production and manufacturing (see Table 2). One notable differentiating feature of biologics is that specific cell lines and processing conditions are typically proprietary. As such, the original product cannot be duplicated precisely, and, consequently, exact copies of biologics are not possible. This is in contrast to small-molecule drugs, which can be copied with insignificant or no variation from the original (Crommelin et al., 2005; Declerck, 2012).

Because of these differences, biosimilars are developed to be highly similar, but not identical, to the licensed biologic. Although minor differences in clinically inactive components between a biosimilar and the originator are expected, for a biosimilar to be approved, the biosimilar must exhibit a high degree of similarity to the originator in terms of safety, purity, and potency (FDA, 2015b). Manufacturing techniques used to produce biologics involve numerous complex processes, all of which may influence biologic and clinical properties of the biologic. As a result, regulatory approval for biosimilars is very different from that for small-molecule generics.

**Regulatory Approval Pathways**

In recognition of differences between biosimilars and small-molecule generics, guidelines specific to biosimilars have been developed by the EMA (2014), FDA (2015b), Health Canada (2016a), and World Health Organization ([WHO], 2009). Although some minor differences exist among the guidelines, requirements for biosimilar approval are generally consistent (Socinski et al., 2015). Approval decisions are made on a case-by-case basis, with the developer of a potential biosimilar and the regulatory agency collaborating to determine which data, analyses, and studies are necessary for the approval process.

The goals of a biosimilar development program are to create a potential biosimilar and establish its similarity to the originator in terms of quality, safety, and efficacy (see Figure 2). Therefore, several types of investigative studies are performed in a stepwise comparative approach to establish that the potential biosimilar is “highly similar” to the originator. Biosimilar development includes analytical studies (in vitro), nonclinical studies (in vivo), human pharmacokinetics studies, and comparative efficacy and safety clinical trials. Analytical studies are conducted first to demonstrate that the potential biosimilar is highly similar to the originator in terms of its chemical and physical properties. Nonclinical studies are then performed to assess the potential biosimilar’s safety and efficacy in animal models. Human pharmacokinetics studies are conducted to evaluate the potential biosimilar’s absorption, distribution, metabolism, and excretion in humans.

### Table 1: Development Status and Patent Expiration Dates for Some Biosimilars in the United States

<table>
<thead>
<tr>
<th>BIOLIGIC</th>
<th>COMMON USES</th>
<th>PATENT EXPIRATION</th>
<th>STATUS</th>
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<tbody>
<tr>
<td>Bevacizumab (Avastin®)</td>
<td>Metastatic colorectal cancer; non-squamous non-small cell lung cancer; glioblastoma; metastatic renal cell carcinoma; persistent, recurrent, or metastatic carcinoma of the cervix; platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer</td>
<td>2019</td>
<td>Application filed</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>Metastatic colorectal cancer, squamous cell carcinoma of the head and neck</td>
<td>2016</td>
<td>Preclinical studies</td>
</tr>
<tr>
<td>Epoetin (Epogen®)</td>
<td>Anemia, cancer, chronic kidney failure</td>
<td>2015</td>
<td>Application filed</td>
</tr>
<tr>
<td>Filgrastim (Neupogen®)</td>
<td>Neutropenia</td>
<td>2013</td>
<td>Approved 2015 (Zarxio®)</td>
</tr>
<tr>
<td>Rituximab (Rituxan®)</td>
<td>Non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis (in combination with methotrexate [Trexall®]), granulomatosis with polyangiitis</td>
<td>2018</td>
<td>Phase III trials</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>HER2-overexpressing breast cancer, HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma</td>
<td>2019</td>
<td>Application filed</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Philippidis, 2014; Stevenson et al., 2017.
BIOSIMILARS

The extent and nature of nonclinical studies and clinical trials depend on the evidence obtained with each previous investigative step. The stepwise approach allows the biosimilar developer and regulatory agencies to determine the extent of residual uncertainty of biosimilarity at each step of development and to identify additional relevant studies and analyses that may be needed to resolve this uncertainty (Christl, 2015). Biosimilar approval is granted based on “totality of the evidence,” which includes the analytical, nonclinical, pharmacokinetics, and clinical data (FDA, 2015b). Data from all stages of development (not just clinical) are important for regulatory approval and medical acceptance.

Considerations for Biosimilar Use

Biosimilars approved and/or in development include products for cancer treatment and supportive care. In the United States, since the first biosimilar was approved by the FDA in 2015 (filgrastim-sndz [Zarxio®]) (FDA, 2015a; Severson, 2015), three others have been approved, and additional biosimilar applications have been submitted (FDA, 2016). As biosimilars move into clinical use for patients with cancer (Roe, 2015), oncology nurses must understand several key considerations related to the use of biosimilars.

Extrapolation

Extrapolation is an important scientific and regulatory principle for biosimilars and is defined as the approval of a biosimilar for use in an indication held by the originator but not directly studied...
in a comparative clinical trial with the biosimilar (FDA, 2015b; Weise, Kurki, Wolff-Holz, Bielsky, & Schneider, 2014). After a biosimilar and originator are compared and biosimilarity is established in a key disease indication, extrapolation of the data to other indications of the originator may be possible. Extrapolation applies all data collected for the biosimilar in one indication to other indications approved for the originator. In addition, extrapolation reduces or eliminates the need for duplicative clinical studies for the biosimilar in multiple indications. For example, a potential biosimilar may be studied in a comparative trial in patients with one type of cancer, but regulatory agencies may permit extrapolation of the data to other types of cancer for which the originator is approved.

Extrapolation is assessed based on appropriate scientific justification, taking into consideration the complete comparability data set for the biosimilar (i.e., totality of evidence from all comparability analyses, not just clinical data) (EMA, 2014; FDA, 2015b; Weise et al., 2012). Evaluation of extrapolation involves assessment of factors such as clinical experience with the originator, what is known about the mechanisms of action, and degree to which the function of the molecule can be analytically characterized (FDA, 2015b). Essentially, if two products are highly similar and have the same mechanism of action in different disease indications, their therapeutic effects (i.e., efficacy, safety, and immunogenicity) should also be similar.

Extrapolation is determined on a case-by-case, agency-by-agency basis. Infliximab is a monoclonal antibody approved to treat various inflammatory conditions, including rheumatoid arthritis, plaque psoriasis, Crohn’s disease, and ulcerative colitis. Biosimilar infliximab (Remsima®, Inflectra®) is the first monoclonal antibody biosimilar approved in several global markets. In reviewing the data for the biosimilar, EMA (2013) included analytical comparative analyses combined with clinical data to demonstrate that pharmacokinetics and therapeutic equivalence in rheumatology conditions would permit extrapolation to all indications of the originator, including Crohn’s disease and ulcerative colitis. In contrast, Health Canada (2014) initially approved biosimilar infliximab for use in rheumatoid arthritis and psoriasis, but not Crohn’s disease or ulcerative colitis because of differences between the biosimilar and originator in some in vitro assays and the absence of clinical studies (Peagan et al., 2014). Subsequently, in June 2016, Health Canada (2016b) extended approval to Crohn’s disease and ulcerative colitis on the basis of new analytical data in support of extrapolation, as well as the fact that observational study data for biosimilar infliximab used in these conditions did not suggest any safety concerns. In the United States, biosimilar filgrastim-sndz was approved by the FDA (2015a) for the five indications of the originator (filgrastim [Neupogen®]) based on safety and efficacy studies conducted in patients with breast cancer receiving myelo-suppressive chemotherapy.

### Interchangeability and Automatic Substitution

Interchangeability is the concept that two products can be exchanged for each other without a significant risk of harm to the patient. Current FDA guidelines may allow some biosimilars to be designated as interchangeable with the originator, provided that additional criteria are met. To be designated as interchangeable, a biosimilar must be “expected to produce the same clinical result as the reference product in any given patient” (FDA, 2009, p. 3). In addition, if administered more than once to an individual, the risk of safety or reduced efficacy of alternating or switching between the biosimilar and the originator “is not greater than the risk of using the reference product without such alternation or switch” (FDA, 2009, p. 3). In January 2017, the FDA (2017a) issued draft guidance for demonstrating interchangeability. In the European Union, interchangeability is not part of the regulatory approval process; therefore, no scientific standards or recommendations have been provided by EMA (2014).

Automatic substitution, the practice by which a product other than the one prescribed is substituted without the informed consent of the prescriber, hinges on the designation of “interchangeable.” In other words, a biosimilar would have to be deemed interchangeable with the originator before automatic substitution could be considered. In the United States, automatic substitution is controlled by state-level mandates, leaving individual states to determine whether a biosimilar can be automatically substituted. Most states are considering specific legislation regarding automatic substitution of biologic products (National Conference

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**TABLE 2.**

**DIFFERENCES BETWEEN BIOLOGICS AND SMALL-MOLECULE DRUGS**

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>BIOLOGIC</th>
<th>SMALL-MOLECULE DRUG</th>
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<tbody>
<tr>
<td>Ease of physiochemical and biologic characterization</td>
<td>Difficult to fully characterize</td>
<td>Easy to fully characterize</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Lower potential</td>
<td>Higher potential</td>
</tr>
<tr>
<td>Manufacturing process</td>
<td>Complex and involving living systems</td>
<td>Straightforward, with predictable chemical and reagent reaction</td>
</tr>
<tr>
<td>Size</td>
<td>Large, with high molecular weight</td>
<td>Small, with low molecular weight</td>
</tr>
<tr>
<td>Stability</td>
<td>More sensitive and vulnerable to environmental factors</td>
<td>Less sensitive to environmental factors</td>
</tr>
<tr>
<td>Structure</td>
<td>Complex</td>
<td>Simple</td>
</tr>
<tr>
<td>Variability</td>
<td>Heterogenous product</td>
<td>Single, defined structure</td>
</tr>
</tbody>
</table>

*Note. Based on information from Camacho et al., 2014; Zelenetz et al., 2011.*
of State Legislatures, 2016). Within clinics, hospitals, and other health systems in the United States, medical staff and pharmacy and therapeutics committees may determine policies on automatic substitution and authorize the therapeutic interchange of biosimilars for originators within their formulary system (Lucio, Stevenson, & Hoffman, 2013).

Pharmacovigilance
Pharmacovigilance describes the detection, assessment, and prevention of adverse effects after a product is approved and marketed. This is important for all biologics, including biosimilars, because of their inherent complexity and sensitivity to manufacturing and environmental changes. These factors make them susceptible to alterations in structure, which can affect safety (Casadevall et al., 2013; FDA, 2015b). Therefore, postmarketing pharmacovigilance is critical to monitoring the safety of biosimilars. In general, regulatory agencies recommend that a pharmacovigilance plan be developed for a biosimilar and consider any known safety signals associated with the use of the originator and its class (EMA, 2014; FDA, 2015b; WHO, 2009).

Biosimilar Naming
Although the International Nonproprietary Names (INN) system defines global standards for the naming of pharmaceuticals, no international consensus exists on the naming of biosimilars. This creates challenges because the naming of drug products, including biosimilars, has consequences for pharmacovigilance (Schellekens, 2009). Each biosimilar product should be readily identified and easily distinguished from the originator and other biosimilars to ensure appropriate use, straightforward identification, precise traceability, and accurate reporting of adverse drug reactions (Casadevall et al., 2013).

The FDA (2017b) has issued guidance on the nonproprietary naming of all biologic products, including originators and biosimilars. Specifically, the FDA advises that originators and biosimilars be given a unique four-letter suffix devoid of meaning, added to the INN. As a hypothetical example, for two products sharing the core name “replicamab,” the proper names may be shown as replicamab-cznm and replicamab-hixf (FDA, 2017b). The goal is to facilitate postmarketing safety monitoring of biologic products by allowing individual products to be tracked at all levels of patient care. In addition, distinct names would help to avoid inadvertent substitution of one drug for another when the therapies are not interchangeable (FDA, 2017b).

The naming of biosimilars is actively discussed by stakeholders worldwide, an indication that a variety of approaches are in effect or under consideration. Similar to the FDA guidance, WHO (2015) is considering a two-part name for all biologic medicines, not just biosimilars. The first part would be the INN, whereas the second part would be a unique four-letter

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**FIGURE 2. DEVELOPMENT PROCESS FOR BIOSIMILARS**

- Reverse engineering to create biosimilar 
- Analytical studies (in vitro) 
- Nonclinical studies (in vivo) 
- Sponsor presents biosimilar data to regulators. 
- Regulators decide whether biosimilar can proceed with comparative clinical studies in patients. 
- Sponsor presents biosimilar pharmacokinetics/pharmacodynamics data to regulators. 
- Pharmacokinetics/pharmacodynamics similarity studies 
- Regulators decide whether biosimilar can enter clinical development. 
- Comparative clinical studies in patients 
- Sponsor presents biosimilar clinical data to regulators. 
- Regulators assess totality of the data and decide whether the biosimilar can be marketed. 
- Regulatory approval 

Note. Based on information from Camacho et al., 2014; Declerck, 2012; Socinski et al., 2015; U.S. Food and Drug Administration, 2015b.
identification code (a “biological qualifier”). Some countries, including Australia and Japan, have approved their own policies for biosimilar naming (Australian Government Department of Health Therapeutic Goods Administration, 2015; Yamaguchi & Arato, 2011). In Europe, biosimilars share the INN that corresponds with that of their reference product; however, EMA recommends that the brand name and packaging of the biosimilar be unique (Alexander, 2014).

**Implications for Nursing**

Biosimilars may offer benefits to patients by increasing access to biologic medications; however, patients may be unaware of or cautious about the use of biosimilars. Many patients want to take greater responsibility for their own health care and be informed about treatment options. Therefore, education of patients and their families is crucial as biosimilars are introduced into oncology practice. Oncology nurses can play a vital role in educating patients by increasing their own awareness of the scientific and quality considerations associated with biosimilars. Patient education focused on biosimilars should contain facts about biosimilars, including their development, safety, and efficacy. A number of resources are available to educate patients about biosimilars, including those from the FDA (e.g., “Biosimilars: More Treatment Options Are on the Way” at http://bit.ly/2SeGSA, “Information for Consumers [Biosimilars]” at http://bit.ly/2SIIJUT) and the International Alliance of Patients’ Organizations (e.g., “Biosimilars Toolkit” at http://bit.ly/29k7SmG). Nurses will also need to know about differences between biosimilars and small-molecule generics and any potential differences between biosimilars and their originators in terms of administration, handling, and/or storage (features not affecting clinical efficacy or safety) to ensure safe patient care with biosimilars. Pharmacists are a resource for additional information about biosimilars, and collaboration between nurses and pharmacists will be critical to optimize medication delivery and administration and to enhance safety. Finally, as with any treatment, nurses are key patient advocates who educate patients about the importance of self-monitoring and reporting of biosimilar-related adverse events.

Oncology nurses also play a vital role in pharmacovigilance for biologics. Nurses are ideally positioned to evaluate and monitor patients, as well as recognize and record adverse events. At the time of administration, precise documentation of the specific biologic product (and lot number) will facilitate linking adverse events to a specific product. By partnering with patients and families and establishing a trusting relationship, oncology nurses can help identify and intervene if patients experience a delayed adverse event.

**Conclusion**

Introduction of high-quality, safe, and effective biosimilars has the potential to provide savings and efficiencies to healthcare systems. As more biosimilars are approved and their use is more widespread, oncology nurses, who play a significant role in the management of patients with cancer, are in a unique position to educate themselves, as well as other clinicians, patients, and families, about biosimilars to ensure accurate understanding and the optimal and safe use of biosimilars.

**REFERENCES**


BIOSIMILARS


