Original Article

Formulary Selection Criteria for Biosimilars: Considerations for US Health-System Pharmacists

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Abstract

Pharmacists will play a key role in evaluating biosimilars for formulary inclusion in the United States. As defined by US law, a biosimilar is a biologic that is highly similar to its reference product, notwithstanding minor differences in clinically inactive components, and should not have clinically meaningful differences from its reference product in safety, purity, and potency. We review biosimilars and the current European Union and US regulatory pathways for biosimilars. Furthermore, we propose a checklist of considerations to ensure that US pharmacists thoroughly evaluate future biosimilars for formulary inclusion. Included in the checklist are considerations related to the availability of preapproval and postapproval safety and efficacy data; differences in product characteristics and immunogenicity between the biosimilar and reference product; manufacturer-related parameters that can affect a reliable supply of quality products; health-system and patient perspectives on product packaging, labeling, storage, and administration; costs and insurance coverage; patient education; interchangeability and differences in the range of indications; and evaluation of institutions' information technology systems.

Key Words—biologics, biosimilars, formulary, pharmacovigilance, reference product

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The first biosimilar was licensed for use in humans in the European Union (EU) in 2006; since that time, a total of 11 distinct biosimilar products have been approved for marketing in the EU under 19 different trade names (2 have since been withdrawn) (Table 1).¹ As more patents for biologic drugs approach expiration, the number of biosimilars entering the market is expected to grow.^{2,3} Yet, as the market awaits the first US biosimilar approval, questions remain about how this new class of drugs will be evaluated for incorporation into US formularies. In the US, the Biologics Price Competition and Innovation Act of 2009 (BPCI Act)—a part of the Affordable Care Act of 2009—provided for an abbreviated

regulatory approval pathway for biosimilars.^{4,5} As defined by the BPCI Act, a biosimilar is a biologic product that is highly similar to its reference product, notwithstanding minor differences in clinically inactive components; a biosimilar is to have no clinically meaningful differences from its reference product in terms of safety, purity, and potency.⁴

Small-molecule generic drugs can be produced using well-defined chemical processes, but biologic drugs are typically large molecules with a complex structure that are manufactured in bioreactors using living cells.⁶ Because the details of manufacturing processes for biologic drugs are often proprietary to the innovator manufacturer, the processes for biosimilar production, such as cell culture, fermentation,

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Table 1. Biosimilars authorized in the European Union^a

Biosimilar	Active substance	Manufacturer ^b	Marketing authorization holder/applicant
Granulocyte colony-stimulating factors			
Biograstim	filgrastim	Sicor Biotech UAB	CT Arzneimittel GmbH
Filgrastim Hexal	filgrastim	Sandoz GmbH	Hexal AG
Filgrastim ratiopharm ^c	filgrastim	Sicor Biotech UAB	Ratiopharm GmbH
Grastofil	filgrastim	Intas Biopharmaceuticals Ltd.; Apotex Nederland BV	Apotex Europe BV
Nivestim	filgrastim	Hospira Zagreb	Hospira UK Ltd.
Ratiograstim	filgrastim	Sicor Biotech UAB	Ratiopharm GmbH
Tevagrastim	filgrastim	Sicor Biotech UAB	Teva Generics GmbH
Zarzio	filgrastim	Sandoz GmbH	Sandoz GmbH
Erythropoietins			
Abseamed	epoetin alfa	Rentschler Biotechnologie GmbH; Lek Pharmaceuticals	Medice Arzneimittel Pütter GmbH & Co. KG
Binocrit	epoetin alfa	Rentschler Biotechnologie GmbH; Lek Pharmaceuticals	Sandoz GmbH
Epoetin Alfa Hexal	epoetin alfa	Rentschler Biotechnologie GmbH; Lek Pharmaceuticals	Hexal AG
Retacrit	epoetin zeta	Norbitec GmbH	Hospira UK Ltd.
Silapo	epoetin zeta	Norbitec GmbH	Stada Arzneimittel AG
Growth hormones			
Omnitrope	somatropin	Sandoz GmbH	Sandoz GmbH
Valtropin ^c	somatropin	LG Life Sciences Ltd.	BioPartners GmbH
Follicle-stimulating hormone			
Bemfola	follitropin alfa	Polymun Scientific Immunobiologische Forschung GmbH; Finox Biotech AG	Finox Biotech AG
Ovaleap	follitropin alfa	Merckle Biotec GmbH; Teva Pharmaceuticals; Europe BV	Teva Pharma BV
Anti-human tumor necrosis factor alpha 2 monoclonal antibody			
Inflectra	infliximab	Celltrion Inc.	Hospira UK Ltd
Remsima	infliximab	Celltrion Inc.	Celltrion Healthcare Hungary Kft

^aAs of September 3, 2014.^bThe same biosimilar from one manufacturer (eg, Sicor Biotech UAB) may be marketed under different brand names.^cMarketing authorization in the EU withdrawn at the request of the marketing authorization holder.

and purification, must be independently developed by the biosimilar manufacturer.⁶ Consequently, there is potential for subtle differences between biosimilars and their reference products.⁶⁻⁸ Thus, biosimilars

will require more extensive evaluation than small molecule generic drugs⁹; the type and amount of clinical data required will be determined on a case-by-case basis.¹⁰

The US Food and Drug Administration (FDA) approval pathway for biosimilars recommends a side-by-side comparison with an approved reference product that should include comparative analytic studies to characterize the product and to identify impurities, animal studies to assess toxicity, clinical studies to assess pharmacokinetics and/or pharmacodynamics and immunogenicity, and additional studies as needed to demonstrate safety and efficacy in the intended conditions of use.^{10,11} Because this abbreviated approval pathway is based on demonstrated similarity to a well characterized, approved reference product, it is expected that some biosimilars will be approved with fewer patients studied and less clinical efficacy and safety data than were required for the reference product, but with more required analytical information (eg, structure and function).^{12,13} However, based on the US definition of a biosimilar, clinical data are not anticipated to significantly differentiate a biosimilar from its reference product. According to the FDA's interpretation of the BPCI Act, a biosimilar can be approved with fewer indications of use, fewer routes of administration, fewer product presentations, and different formulations and container closures than the reference product.¹⁴ Although no clinically relevant differences in safety or efficacy between a biosimilar and its reference products are permitted, there could be some differences in immunogenicity profiles that are not considered clinically relevant; in some cases, these differences may only become apparent through postapproval safety monitoring.¹⁰ Therefore, it is important for pharmacists to consider additional product- and manufacturer-related parameters when evaluating biosimilars for potential formulary inclusion.⁹

Given the unique nature of biosimilars and their abbreviated regulatory pathway, formulary review and therapeutic interchange options will need to be considered for this class of medicines. This review provides an overview of biosimilars, offers insights into EU and US regulatory pathways for biosimilars, and recommends a checklist of considerations for pharmacists when evaluating biosimilars for inclusion in a US health-system formulary.

REGULATORY PATHWAYS FOR BIOSIMILARS AND BIOLOGIC DRUGS

The legal basis for the approval of biosimilars in the EU was established in 2001 (EU Directive 2001/83/EC, as amended).^{15,16} The EU regulatory approach for biosimilars, including recombinant biologic drugs and monoclonal antibodies, is outlined in a series of guidelines issued by the Committee for Medicinal Products for Human Use of the European

Medicines Agency (EMA).¹⁷⁻²⁰ The EMA guidelines, which provide recommendations for the analytic characterization of biosimilars, as well as nonclinical and clinical studies, stipulate that comparable clinical efficacy and safety versus the approved reference product must be demonstrated for approval.^{18,21} Furthermore, the EU regulatory approach emphasizes that the evaluation of biosimilars is inherently more difficult than the evaluation of chemically derived generic products, which are assessed based on the demonstration of bioequivalence with a reference product through bioavailability studies.¹⁷

In some aspects, the US regulatory pathway for biosimilars models the EU pathway, which has generally been regarded as successful.^{3,12} Consistent with the EU regulatory approach for biosimilars, the US approach (per the BPCI Act) generally requires analytical, preclinical, and clinical comparison of a proposed biosimilar and its reference product to demonstrate biosimilarity, although components of these comparisons may be waived.⁴ After the passing of the BPCI Act in February 2012, the FDA issued 3 draft guidance documents with recommendations aimed at guiding manufacturers in demonstrating biosimilarity to a reference product.^{10,11,14} These documents outline the FDA's approach for evaluating biosimilarity with respect to structure; biological function; toxicity in animal studies; human pharmacokinetic and pharmacodynamic profiles; and clinical immunogenicity, safety, and efficacy.¹⁰ The FDA draft guidance on quality considerations in demonstrating biosimilarity provides recommendations for manufacturers on analytic studies to assess similarity in structure, posttranslational modifications, and functional activity of a proposed biosimilar versus its reference product.¹¹

Analytic assays and physicochemical and functional characterization studies are recommended to demonstrate quality and to define a biosimilar product's identity, quantity, purity, potency, and consistency in comparison with its reference product.¹¹ Per this guidance, analytic assays to demonstrate product quality may include side-by-side assessment of molecular weight, molecular complexity (ie, tertiary structure and posttranslational modifications of proteins), heterogeneity (eg, glycoform variants), biological activity, immunochemical properties (eg, kinetics of receptor binding), product- and process-related impurities, product stability, and degradation profiles. The FDA draft guidance also notes that the biosimilar manufacturer should describe the capabilities and limitations of the analytic assays used to demonstrate quality.¹¹ Furthermore, demonstration of product quality and

biosimilarity may require preclinical studies as well as studies that compare the toxicity, pharmacokinetics, and pharmacodynamics of a proposed biosimilar with its reference product.¹⁰ Unlike the current regulatory approach to biosimilars in the EU, the BPCI Act provides the opportunity for biosimilar manufacturers to seek an “interchangeable” designation in the United States, which reflects the FDA’s determination that the biosimilar may be “substituted for the reference product without the intervention of the health care provider who prescribed the reference product”⁴ (see Hospital and Patient Considerations section). Such substitution may be regulated by individual US states through their pharmacy acts.

Although the regulatory pathway for biosimilars in the United States has not yet been finalized, the first biosimilars are expected to achieve FDA approval and enter the US market in the near future, after the loss of data exclusivity and patent expiration for a number of innovator products (Table 2).^{4,22} Although currently there are no approved biosimilars in the United States, the FDA recently approved the granulocyte colony-stimulating factor tbo-filgrastim (Sicor Biotech UAB, a member of Teva Corporation; Vilnius, Lithuania) for the treatment of severe neutropenia in selected patients with nonmyeloid malignancies.²³ Because tbo-filgrastim was approved through the stand-alone Biologics License Application (BLA) pathway, it is not classified as a

biosimilar.²³ In addition, the FDA has assigned a distinguishable nonproprietary name for this biologic product. The pending entry of biosimilars into the US market, and the differences in their regulatory approval compared with innovator biologic drugs, underscores the importance of pharmacists in identifying critical issues for consideration during formulary review of biosimilars.

CONSIDERATIONS FOR PHARMACISTS EVALUATING BIOSIMILARS FOR FORMULARY INCLUSION

As Pharmacy and Therapeutics (P&T) Committees (or similar committees charged with institutional formulary decision making) review biosimilars for formulary inclusion, pharmacists will play a critical role in evaluating product- and manufacturing-related parameters that are unique to biosimilars and their abbreviated regulatory pathway. Key elements of biosimilar formulary review include evaluation of parameters related to safety and efficacy as well as manufacturer considerations and hospital and patient considerations, such as economic impact, from both a health-system and a patient perspective. We therefore propose a checklist of these considerations for use by pharmacists as a part of their formulary review of biosimilars (Table 3). These evaluation parameters are particularly important as P&T Committees consider the range of indications for which a given biosimilar may be used within their organization.

Table 2. Sample of biologic drugs with pending or past exclusivity dates in the United States⁴⁸

Biologic drug	Original license applicant	FDA approval date
Adalimumab	Abbott Laboratories	December 2002
Bevacizumab	Genentech, Inc.	February 2004
Cetuximab	ImClone Systems, Inc.	February 2004
Darbepoetin alfa	Amgen Inc.	September 2001
Epoetin alfa	Amgen Inc.	June 1989
Etanercept	Immunex Corp.	November 1998 / September 2004
Filgrastim	Amgen Inc.	February 1991
Infliximab	Janssen Biotech, Inc.	August 1998
Interferon alfa-2b	Schering Corp.	June 1986
Interferon beta-1a	Biogen Idec, Inc.	May 1996
Interferon beta-1b	Bayer Healthcare Pharmaceuticals Inc.	July 1993
Interferon gamma-1b	InterMune, Inc.	February 1999
Pegfilgrastim	Amgen Inc.	January 2002
Peginterferon alfa-2a	Hoffmann-La Roche, Inc.	October 2002 / September 2011
Peginterferon alfa-2b	Schering Corp.	January 2001
Rituximab	Genentech, Inc.	November 1997
Trastuzumab	Genentech, Inc.	September 1998

Table 3. Considerations for pharmacists evaluating biosimilars for formulary inclusion

Safety and efficacy	
Product characteristics ¹¹	<ul style="list-style-type: none"> • Are there any differences in formulation or excipients of the biosimilar under consideration versus the reference product? • Are there any differences in compatibility (eg, injection pain, interference with laboratory assays) between the biosimilar under consideration and the reference product?
Clinical data ¹⁰	<ul style="list-style-type: none"> • Is the amount of available clinical data sufficient for the indications being considered for formulary inclusion? • Have postapproval studies been evaluated? • Are relevant clinical data from international studies available for review?
Immunogenicity ¹⁰	<ul style="list-style-type: none"> • Are there any differences in the immunogenic profiles between the biosimilar under consideration and the reference product with respect to the incidence of <ul style="list-style-type: none"> – Infusion reactions? – Neutralizing antibodies?
Manufacturer considerations	
Medication availability ³¹	<ul style="list-style-type: none"> • Are there any differences in clinic administration and/or retail availability between the biosimilar under consideration and reference product that may affect the overall availability of the products? • Does the manufacturer have a process to ensure a reliable and uninterrupted supply of the product? <ul style="list-style-type: none"> – Does the manufacturer maintain adequate levels of reserve product in stock? • Does the manufacturer have the ability to increase production at another location, if necessary, to meet demand?
History of shortages and recalls ³¹	<ul style="list-style-type: none"> • Has the manufacturer experienced shortages of this product or other products? <ul style="list-style-type: none"> – If so, what was the cause and how often have shortages occurred? • Has the product ever been recalled because of quality concerns? • Has the manufacturer had other products recalled as a result of quality concerns?
Handling practices ³¹	<ul style="list-style-type: none"> • Does the manufacturer adequately document and maintain controlled temperature during distribution of the product? • Does the manufacturer take the necessary steps to prevent exterior contamination of vials?
Supply chain security	<ul style="list-style-type: none"> • Does the manufacturer apply and document adequate security technologies for product authentication, warehouse/cargo security, and market surveillance to detect potential product diversion or counterfeits? <ul style="list-style-type: none"> – Are there any differences between the biosimilar under consideration and reference product with respect to security systems and procedures at the warehouse, pallet, truck, and carrier level?
Anticounterfeit protection	<ul style="list-style-type: none"> • Does the manufacturer have a program in place to guard against counterfeiting?
Hospital and patient considerations	
Packaging and labeling	<ul style="list-style-type: none"> • Are the containers, packaging, and labeling well-designed and easy to read? • Are there any differences in packaging between the biosimilar under consideration and reference product? • Are there any differences in warnings on the label regarding handling between the biosimilar under consideration and reference product?

(continued)

Table 3. Considerations for pharmacists evaluating biosimilars for formulary inclusion (CONT.)

Hospital and patient considerations	
Product storage	<ul style="list-style-type: none"> • Are there differences in shelf life or storage requirements between the biosimilar under consideration and reference product? • Are there any differences in light sensitivity between the biosimilar under consideration and reference product? • Do any differences in storage conditions offer an advantage or disadvantage in terms of patient care? • Will both the biosimilar under consideration and reference product be stocked based on differing indications between the products or for patients admitted on the reference product? <ul style="list-style-type: none"> – If so, how will the biosimilar under consideration and reference product be stored to eliminate the potential for a dispensing error? • Are there any differences in product configuration (eg, size or shape) between the biosimilar under consideration and reference product that could impact compatibility with a robotic compounder?
Product administration	<ul style="list-style-type: none"> • Are there any differences in the delivery system or device between the biosimilar under consideration and reference product (eg, autoinjector)? <ul style="list-style-type: none"> – Does the labeling for the biosimilar under consideration include information on delivery? – What is the plan for educating patients receiving a biosimilar with a different delivery system/device from the reference product? • Does the biosimilar under consideration have fewer approved routes of administration than the reference product? • If provided in vials, are there any differences in the amount of excess product between the biosimilar under consideration and reference product? • Are there any differences in pharmacy technician time and techniques for compounding between the biosimilar under consideration and reference product? • Are there any differences in timing of administration or patient experience that may affect patient and nurse preference between the biosimilar under consideration and reference product?
Interchangeability ^{4,5,14,31}	<ul style="list-style-type: none"> • Does the biosimilar under consideration meet clinical and regulatory criteria to be freely substituted for the reference product (and vice versa)? • Should a therapeutic equivalence program be established for use within the hospital or health system and be approved by the P&T Committee and medical staff? • Will patients who are taking the reference product at home be required to convert to the biosimilar under consideration? <ul style="list-style-type: none"> – If yes, how will care transitions be managed? – Will policies be developed to specifically manage care transitions?
Variety of indications ⁵	<ul style="list-style-type: none"> • Is the reference product currently being used for multiple indications? <ul style="list-style-type: none"> – If so, is the biosimilar under consideration being evaluated for all those same indications, including FDA-approved indications and those considered standard of care?
Product naming ⁵	<ul style="list-style-type: none"> • How is the specific product recorded in the medication dispensing documents? • Will the selected name ensure traceability of adverse events to the specific product? • Are any special procedures required to ensure traceability of the biosimilar under consideration?
Information technology support	<ul style="list-style-type: none"> • Does the hospital have a robust information technology infrastructure to support <ul style="list-style-type: none"> – Distinguishing the biosimilar under consideration from the reference product during order entry? – Tracking which product was administered (biosimilar under consideration versus the reference product)? • Is the labeling of the biosimilar under consideration compatible with the facility's current technology (eg, bedside barcode scanning)?²⁴³

(continued)

Table 3. Considerations for pharmacists evaluating biosimilars for formulary inclusion (CONT.)

Hospital and patient considerations	
Economic considerations ^{4,5}	<ul style="list-style-type: none"> • Are reimbursement support and other programs (eg, product replacement, copay assistance, and insurance denial support) available for uninsured/underinsured patients receiving the biosimilar under consideration? <ul style="list-style-type: none"> – If not, how will this affect the overall cost of adding the biosimilar under consideration to formulary? • Will all government and commercial payer policies apply equally to both the reference product and the biosimilar under consideration? • Are there any differences between the biosimilar under consideration and reference product with respect to the 340B Drug Pricing Program? • Are there any differences between the biosimilar under consideration and reference product with respect to ease of access to the product (eg, based on payer requirements for preauthorization)? • Are there financial and/or legal risks of using the biosimilar under consideration for an unapproved indication for which the reference product has approval? • Does the difference in cost for the biosimilar under consideration versus the reference product support a full formulary conversion?
Patient education ⁵	<ul style="list-style-type: none"> • Does the manufacturer provide patient education materials at a 6th grade reading level? <ul style="list-style-type: none"> – Do materials appropriately distinguish biosimilars and generics? • Is it necessary to develop materials for educating patients on the interchangeability of biosimilars?

Safety and Efficacy

Product Characteristics

P&T Committees routinely assess safety and efficacy data from clinical studies for all drugs for formulary reviews; however, there are unique considerations for evaluating biosimilar clinical studies. Clinical studies supporting biosimilar development are intended as sensitive tests of similarity to the reference product and are not designed to reestablish safety or efficacy. The FDA draft guidance indicates that clinical studies should be designed to “demonstrate that the proposed product has neither decreased nor increased activity compared to the reference product” and that clinical studies of biosimilars—including assessment of immunogenicity and pharmacokinetics or pharmacodynamics—should be sufficiently designed “to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed.”¹⁰

In Europe, one analytical evaluation of 2 marketed biosimilar epoetin products showed that the products differed in their protein content and isoform profiles and that in vivo potency of *Binocrit* (epoetin alfa; Sandoz GmbH, Kundl, Austria) and *Retacrit* (epoetin zeta; Hospira UK Limited, Warwickshire,

United Kingdom) was approximately 11% and 14% lower, respectively, compared with the potency of their biologic reference product, *Eprex* (epoetin alfa; Janssen-Cilag GmbH, Neuss, Germany).²⁴ However, a subsequent population-based analysis demonstrated that in clinical practice, the doses of epoetins actually administered were quite similar (the median delivered dose of biosimilar epoetin alfa was slightly higher [6%] compared with the originator products).²⁵

As with any biologic medicine, ongoing postapproval assessment may further characterize differences between a biosimilar and its reference product that were not fully characterized during testing for biosimilar registration. FDA guidance indicates that comparative clinical “safety and effectiveness data will be necessary to support a demonstration of biosimilarity if there are residual uncertainties about the biosimilarity of the two products based on structural and functional characterization, animal testing, human PK [pharmacokinetics] and PD [pharmacodynamics] data, and clinical immunogenicity assessment.”¹⁰ It should be noted that biosimilars will be approved by the FDA as safe and effective; therefore, pharmacists should conduct their review of the available biosimilar data in comparison to the characteristics of the reference product in this context. Any differences in safety, efficacy, product-specific characteristics

(eg, formulation and excipients), or compatibility (eg, injection pain and interference with laboratory assays) should be assessed in terms of how the products will be used in the specific patient populations, as should the potential need for dose adjustments based on possible differences in renal or liver clearance or formulation. Pharmacists can also analyze and critique the product prescribing information and complete their own safety assessment.

Clinical Data and Immunogenicity

Pharmacists will need to evaluate the amount and quality of available clinical data to support registration of a biosimilar by regulatory authorities, particularly for the indications under consideration for formulary inclusion, and the type of postapproval data that may be available (Table 3). This should also include review of clinical data to support registration of the biosimilar outside the US and international postapproval data, if available. Given the difficulty in identifying rare adverse events (AEs) associated with a drug during clinical trials, postapproval safety surveillance—pharmacovigilance—is an important tool for evaluating a drug's safety profile and for informing decisions needed to minimize risks.²⁶

The importance of monitoring biologics for changes in immunogenicity is exemplified by the increase in cases of antibody-mediated pure red cell aplasia (PRCA) in Europe from 2002 to 2003 among patients with chronic renal failure who received recombinant human erythropoietin. The majority of the PRCA cases during that time have been linked to a specific preparation of erythropoietin (*Eprex* [epoetin alfa]) and have been associated with the formulation and increased immunogenicity resulting from organic leachates from uncoated rubber syringe stoppers.²⁷ It should be noted, however, that *Eprex* was approved as a new biologic, not a biosimilar.

Pharmacovigilance requires accurate and complete assignment of a potential safety signal to a particular product. The importance of accurately associating AEs with a biologic drug is heightened with multiple sourced biologics, because slight product differences could result in clinically important effects.^{2,6,8,12} This is illustrated by the cases of antibody-mediated PRCA in Thailand in 2008 following treatment with multiple sourced, noncomparable recombinant human erythropoietin products in the absence of rigorous quality standards for biosimilars in that country.^{28,29} In a study assessing the development of antibodies against recombinant human erythropoietin in Thailand, 23 of

30 patients with chronic renal failure who received one of a number of immunogenic multiple sourced recombinant human erythropoietin products and subsequently experienced a loss of efficacy tested positive for neutralizing antibodies; however, the study was unable to identify which specific products were associated with the development of antibody-mediated PRCA.²⁸

Immunological events associated with biosimilars may not be observed for months after the introduction of the product.³⁰ Therefore, data on immunogenic events on newly introduced biosimilar products may be limited initially. Pharmacists should support product safety monitoring systems by fostering accurate medical records for biologic therapies and collaborating with physicians on forensic evaluations of adverse drug reactions. They should also review available preapproval and postapproval clinical data that may indicate any differences in immunogenic profiles (eg, infusion reactions, neutralizing antibodies, or loss of efficacy) between approved biosimilars and their reference products.

Manufacturer Considerations

Medication Availability, History of Shortages and Recalls, and Handling Practices

Given the concerns of immunogenicity when different versions of a biologic medicine are used, it is desired to have a reliable and consistent supply of these medications. Accordingly, supply chain considerations are important manufacturer parameters to evaluate when reviewing drugs for potential formulary inclusion (Table 3). Manufacturers should be expected to make such information available to facilitate formulary review. Pharmacists should inquire whether the manufacturer has a process to ensure a reliable and uninterrupted supply of the product and whether it maintains adequate production and stock to support demand.³¹ Pharmacists should also determine whether manufacturers maintain sufficient safety stock and have backup or multisite manufacturing capabilities in the event of unexpected disruptions at the primary manufacturing facility.^{9,32} Drug shortages, such as the recent shortages of methotrexate, cytarabine, and liposomal doxorubicin, may result in the rationing or delay of critical treatments and the use of less efficacious or more expensive drugs.³²⁻³⁷ To ensure confidence in the integrity and reliability of drug supply, formulary review of a biosimilar should include evaluation of the manufacturer's history of shortages and recalls associated with product

quality.⁹ Indeed, failure of quality management in the production of the finished dosage form of drugs has been cited as the primary driver of drug shortages.³⁸ Drug shortages caused by supply delays, diminished production capacity, and discontinuations of a product by the manufacturer may also be quality-related disruptions in the production line. Additionally, shortages related to quality issues such as particulates and contamination may indicate ineffective quality control processes, warranting careful consideration when evaluating a manufacturer's capability to reliably maintain a quality drug supply.

Pharmacists should also consider a manufacturer's handling practices of products, including an evaluation of the manufacturer's documentation of controlled temperature during distribution, as well as the steps the manufacturer takes to prevent contamination of the exterior of product vials.^{9,32}

Supply Chain Security and Anticounterfeit Protection

Supply chain security and anticounterfeit protection represent additional important considerations for pharmacists evaluating biosimilars for formulary inclusion.^{9,32} Among the key questions for consideration is whether the manufacturer can document and ensure a high level of protection against interference with the supply chain by illegal drug diversion and counterfeit drugs. Such measures may include the use of forensic security technologies for product authentication; security systems and procedures at the warehouse, pallet, truck, and carrier level; and market surveillance to detect counterfeits and monitor for product diversions. Recent investigations regarding the distribution of counterfeit products in the United States highlight the need for anticounterfeit measures to safeguard patients and ensure product quality.³⁹

Hospital and Patient Considerations

During formulary review of a biosimilar, pharmacists should weigh considerations from the hospital and patient perspectives regarding product packaging, labeling, storage, and administration. Pharmacists should also consider implications of interchangeability, multiple indications of products, product naming, and information technology requirements. Additionally, the economic impact of adding any drug to the formulary, whether a biosimilar or its reference product, should be considered from both the hospital and patient perspectives, including costs and insurance coverage issues and the need for patient education to support use of the biosimilar.

Product Packaging, Labeling, Storage, and Administration

Pharmacists should consider the clarity and safety of the product packaging and labeling and ensure that products from various manufacturers and multiple products from the same manufacturer can be differentiated. The label should be clear and easy to read, and the product container and delivery devices should be well-designed for use by health care professionals and patients. Pharmacists should consider whether there are differences between the biosimilar and its reference product, or between biosimilars, in packaging, shelf life, storage temperature, light sensitivity, or routes of administration that might lead to confusion or errors that could compromise product integrity or patient safety. For example, it will be important for pharmacists to consider whether the biosimilar (or multiple biosimilars) and its reference product (assuming both products are approved formulary agents) will be stocked based on differences in indications and how the products will be stored to reduce the risk of dispensing errors. Additionally, pharmacists should evaluate the biosimilar's compatibility with the institution's compounding technology and identify differences in technician time and techniques that may be required compared with the reference product or other biosimilars of the reference product. Pharmacists should consider potential differences between the products in timing of administration or patient experience. For example, increased pain on administration related to the formulation could negatively affect patients' and nurses' experiences with the biosimilar.

Interchangeability

According to the BPCI Act, biosimilar manufacturers will have the opportunity to pursue the designation of interchangeability in the United States. This designation reflects the FDA's determination that the pharmacist may substitute the prescribed reference product with the interchangeable biosimilar without the prescriber's intervention.⁴ The criteria for a biosimilar that is to be designated as interchangeable are higher than those of a standard biosimilar versus the reference product.¹² In addition to demonstrating biosimilarity, based on the BPCI Act, FDA approval for interchangeability requires that the biosimilar "can be expected to produce the same clinical result as the reference product in any given patient" and that if "administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biologic product and the reference product

is not greater than the risk of using the reference product without such alternation or switch.”⁴ Thus, interchangeability is distinct from therapeutic interchange, which is defined as the dispensing of a drug that is therapeutically equivalent to the prescribed drug, yet chemically different.^{31,40} Furthermore, interchangeable biosimilars must have highly similar pharmacokinetics and toxicities and the same mechanism of action as their reference product,⁴ whereas drugs used in therapeutic interchange may differ in these parameters.⁴⁰ Although authorization by the prescriber may not be required to substitute an interchangeable biosimilar for its reference drug, therapeutic interchange may require prior authorization based on processes established by P&T Committees. It will be important to determine whether there are any applicable state requirements for notifying prescribers of substitutions when a biosimilar is substituted; such requirements, if they exist, may only apply to dispensing in the community or retail setting.

Many health systems use therapeutic interchange programs for biologic products such as human insulins and intravenous immunoglobulin products. For health systems considering therapeutic substitution of a biosimilar that does not have the interchangeable designation, members of the P&T Committee will need to conduct a thorough evaluation to assess the risks and benefits of internally assigning the designation.

Biosimilar interchangeability differs from generic substitution, which is defined as the substitution of a reference drug with its generic version that has identical active ingredients and the same strength, concentration, dosage form, and route of administration.³¹ Generic substitution is typically prospectively authorized by the prescriber, and the prescriber is not notified of generic substitution upon dispensing. As P&T Committees review biosimilars for formulary inclusion, they should consider whether the biosimilar has the FDA interchangeability designation and, if so, for which indications. P&T Committees will also need to consider whether an interchangeable biosimilar under formulary review has been approved as interchangeable for all of the approved indications of the reference product versus only selected indications and whether interchange should be accompanied by communication with the prescriber. Moreover, it will be important for pharmacists and P&T Committees to address the issue of transitions of care and to consider implications of policies and practices for patients who receive a given product (ie, biosimilar or reference product) in a particular care setting (ie, outpatient or inpatient) and then transition to home or a different care setting.

Pharmacists will need to consider the operational details and the extent of information technology support necessary to manage and accurately track an interchangeable biosimilar approved for a variety of indications, assuming both products are approved as formulary agents, particularly given the added operational challenge of managing an interchangeable biosimilar if the naming system does not easily distinguish the biosimilar from its reference product (see *Product Naming and Information Technology Support* section).

Variety of Indications

If a reference product is currently used for multiple indications within the health system, it will be important for pharmacists to consider whether the biosimilar is being evaluated for formulary inclusion for all indications of the reference product, including FDA-approved indications and those considered standard of care.

The FDA has addressed the issue of licensure of a proposed biosimilar product for fewer than all the conditions of use for which the reference product is licensed.¹⁴ Additionally, guidance is provided on extrapolation of clinical data intended to demonstrate biosimilarity in one condition to support licensure in one or more additional conditions for which the reference product is licensed.^{10,14} According to the FDA guidance, “the potential exists for the biosimilar product to be licensed for one or more additional conditions of use for which the reference product is licensed. However, the applicant would need to provide sufficient scientific justification for extrapolating clinical data to support a determination of biosimilarity for each condition of use for which licensure is sought.”¹⁴ In some cases, P&T Committees will need to address uses of a biosimilar not approved by the FDA. For example, if an institution is already using a reference product for indications not currently approved by the FDA, the P&T Committee will need to consider which indications or usage restrictions it will approve for biosimilars under consideration.

Product Naming and Information Technology Support

The challenge of biosimilar pharmacovigilance may be magnified by the potential for interchangeability and lack of clarity about how biosimilars will be named. Accurate traceability of AEs is dependent on product naming, labeling, and the approach for recording a specific product in the drug-dispensing records. If the naming approach does not allow products to be readily distinguished, it may be challenging to accurately

trace AEs via lot numbers and National Drug Codes (NDCs), because these identifiers are not used in all health systems.² In contrast with small-molecule generic drugs, which use the same nonproprietary name as their reference product, the naming of biosimilar drugs is complicated by the fact that they may not be identical to their reference product. Based on policies of the World Health Organization (WHO), which assigns international nonproprietary names (INNs), Greek letter suffixes have been assigned to epoetin biosimilars to indicate differences in glycosylation. For example, one distinct epoetin biosimilar marketed under 2 trade names in the EU was assigned the INN epoetin zeta, indicating differences in glycoforms.^{41,42} However, this approach has not been followed consistently, as some epoetin biosimilar manufacturers did not seek an INN from the WHO but rather adopted the same INN as the reference product despite differences in glycosylation.⁴¹ Although the naming conventions for biosimilars have not yet been finalized, EMA and FDA officials have acknowledged the importance of a consensus on biosimilar naming that allows products to be readily identified and distinguished for robust pharmacovigilance and tracking.^{12,17}

As part of their review of biosimilars for formulary inclusion, pharmacists should consider how the biosimilar naming approach will affect tracking and tracing of AEs associated with a particular dispensed biosimilar, as well as the capabilities of institutional computer systems. Pharmacists should ensure that the hospital information technology system is capable of distinguishing among multiple versions of biologic products and biosimilars such that it can accurately track the specific drug(s) a patient received and can trace reported AEs under the current naming system. Tracking and tracing of biosimilars and reference products is critical to ensure that the AE in question is attributed to the correct drug. The use of distinct names for biosimilars is one of several ways pharmacists will track the product; however, it may be necessary to implement special procedures if biosimilars have the same name as the reference product. Although bedside barcode scanning and NDC data may lessen concerns regarding drug tracking by allowing nurses to automatically document the specific drug administered and enter it into an electronic medication administration system,⁴³ this technology is not currently available to all health care providers.

Economic Considerations

According to some reports, biosimilars have the potential to change the pharmaceutical landscape by reducing the estimated development costs through marketing approval from more than \$800 million for a new

innovator drug to \$100 to \$200 million for a biosimilar.^{44,45} Thus, biosimilars are expected to cost less than their reference products. The economic impact of biosimilars should be considered from both the payer and patient perspectives during formulary review.^{46,47} Consideration of reimbursement support and government and commercial payer policies for biosimilars compared with their reference products is an important component of formulary review. In particular, any cost differences between biosimilars and their reference products should be carefully evaluated in consideration of differences in manufacturer assistance programs. Institutions may prefer not to switch to a biosimilar if the manufacturer does not provide an assistance program similar to that of the reference product. P&T Committees will need to consider the cost pressures from payers to use less expensive products on the formulary and coverage of these products outside of the health system and in transitions of care. It will be important to understand how any differences between the reference product and biosimilar in payer requirements and prior authorizations will affect access to the biosimilar under consideration. The out-of-pocket copayment or coinsurance costs to the patient should also be considered in the context of a formulary decision. Thus, rather than considering only the acquisition cost alone, P&T Committees should consider the total cost of using any drug, whether a biosimilar or innovator drug, including costs related to patient and institutional support programs, medical information support, technology changes necessary to ensure tracking and traceability of AEs, and costs that could result if the manufacturer cannot maintain adequate drug supply. Costs of monitoring the response to therapy and the potential for underwriting such costs, although not direct hospital costs, should also be factored into the decision about adding a biosimilar to the hospital formulary. Finally, it will be important to understand whether a difference in the total cost between available biosimilars or other biologics and the reference product will support a full formulary conversion to the biosimilar.

Patient Education

As a part of the P&T Committee's broad evaluation of biosimilars for formulary inclusion, patient education materials provided by the manufacturer should be reviewed, if available. If appropriate patient education materials are not available, the committee should determine whether materials will need to be developed to educate patients on proper use and important considerations, such as interchangeability of the biosimilar and transitions of care.

SUMMARY

Pharmacists will play a key role in evaluating biosimilars for inclusion into the formulary. A number of product and manufacturer parameters will need to be weighed during this process, including parameters related to the assessment of product safety and efficacy and manufacturer considerations. Pharmacists will also need to review health-care system and patient considerations, including economic considerations (eg, cost and coverage concerns) and issues surrounding use of biosimilars and reference products following transitions of care between the inpatient and outpatient setting. To aid pharmacists in reviewing each of these topics, we propose the use of a checklist of considerations for evaluating biosimilars for formulary inclusion (Table 3).

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