Evaluation of Biosimilars for Formulary Inclusion: Factors for Consideration by P&T Committees

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INTRODUCTION

Health care professionals (HCPs), particularly P&T committee members, will play a key role in driving the adoption of biosimilars by the U.S. health care system. Through the application of formulary and practice management tools and principles, P&T committee members will provide leadership in the use of these agents. Key elements of biosimilar formulary review will include evaluation of clinical parameters (indications, clinical data, immunogenicity); product characteristics (nomenclature, supply chain, packaging/labeling), and institutional considerations (substitution, pharmacovigilance, cost/reimbursement, patient/provider education, tracking and information system implications). However, biosimilars have unique characteristics compared with small-molecule generic drugs that pharmacists and other P&T committee members must understand to ensure the safe and optimal use of these medications. To assist P&T committees in the thorough evaluation of biosimilars for formulary inclusion, this article explores these and other considerations.

THE INCREASING ROLE OF BIOLOGICS IN HEALTH CARE

Since the introduction of recombinant human insulin in 1982, the use of biologic medications has continuously increased. Biologic products such as epoetin, pegfilgrastim, rituximab, infiximab, bevacizumab, and trastuzumab have been among the top 15 medications used in hospital and clinic settings. By 2016, 10 of the 20 top-selling drugs worldwide are expected to be biologics. In addition, numerous biologics are currently in the pharmaceutical industry’s investigational drug pipeline. Health care systems have also become increasingly dependent on generic conventional drugs. In 2010, 78% of all prescriptions dispensed by retail pharmacies were for generics. Between 2002 and 2011, the availability and use of generic drugs saved an estimated $1 trillion for the U.S. health care system. However, while small-molecule, chemical generic medications have moderated the growth in drug costs, rising drug expenditures have increasingly become associated with branded biologics. Spending on biologics is expected to continue to grow more than 10% per year until key biosimilars become available. As more patents for costly branded biologics expire, the number of biosimilars entering the market will grow. This increase in competition among manufacturers, reduce prices, and improve patient access to these products. The introduction of biosimilars is projected to save as much as $25 billion in drug costs by 2018.

In July 2014, the first application for approval of a biosimilar was submitted to the U.S. Food and Drug Administration (FDA) under the abbreviated 351k pathway that was created in the Biologics Price Competition and Innovation Act (BPCIA), which was part of the Patient Protection and Affordable Care Act (PPACA). On July 24, 2014, Sandoz announced that the FDA had accepted its application for its biosimilar to Neupogen (filgrastim). On January 7, 2015, the FDA Oncologic Drugs Advisory Committee unanimously recommended the approval of this drug. On March 6, 2015, the FDA approved the Sandoz follow-on biologic, which has been given the “placeholder” name filgrastim-sndz, making it the first biosimilar available in the U.S. Several other applications for biosimilar approvals have been submitted to the FDA under the abbreviated 351k pathway. In August 2014, Celltrion filed an application for approval of its biosimilar to Remicade (infliximab). In December 2014, Hospira and Apotex submitted applications for biosimilars to Epogen/Procrit (epoetin alfa) and Neulasta (pegfilgrastim), respectively. These biosimilars may also be approved this year.

BIOSIMILAR REGULATORY CONSIDERATIONS

Federal Regulatory Considerations

The FDA was granted legal authority to approve follow-on versions of previously approved biologics through an abbreviated approval pathway in March 2010, under the BPCIA. The agency published guidance defining requirements for the approval of biosimilars in February 2012; this guidance was finalized on April 28, 2015. In comparison, biosimilars have been on the market for seven years or longer in Europe, Japan, Australia, and other places. P&T committee members must understand the differences in the approval pathways for branded and follow-on biologics so they can evaluate the labeling associated with each medication. The 351k guidelines for biosimilar approval aim to strike a balance between the need for scientific comparability, safety and efficacy testing, and a less costly pathway to approval. According to the law, a biosimilar must demonstrate that it is comparable to its “originator” or “reference” product (the branded biologic). To demonstrate comparability, a biosimilar must be proven to lack clinically meaningful differences from its reference product in purity, safety, and potency. If desired, biosimilar sponsors can instead opt to seek approval through the full biologics licensing application (BLA) pathway, which requires the submission of more extensive clinical data.

In contrast, new originator biologic products must be approved through the full BLA regulatory pathway. Some manufacturers may produce “biobetters,” which are also based on originator products. These are biologics that are specifically engineered to have improved characteristics compared to an originator agent with respect to clinical performance, such as an extended half-life, increased potency, reduced toxicity, or a preferred route of administration. Biobetters must seek approval through the full BLA regulatory pathway. Importantly, the FDA’s approval of a biosimilar does not necessarily mean the medication is therapeutically equivalent to the corresponding branded biologic. Instead, the FDA can designate a biosimilar as “interchangeable.” This means that...
the biosimilar is not only comparable to the branded originator biologic; it is also proven to be therapeutically equivalent and is expected to produce the same clinical results. The FDA has not yet definitively established the regulatory guidelines for the interchangeable designation. However, because the biosimilar 351k regulatory pathway is abbreviated, the clinical data required for a designation of interchangeability by the FDA is expected to be limited compared with the regulatory approval of an originator biologic through the full BLA pathway.

State Regulatory Considerations

Health system pharmacists need to be aware of state requirements concerning substitution and interchange for biosimilars. According to the BPCIA, federal law states that biosimilars designated by the FDA as interchangeable are considered to be therapeutically equivalent and may be substituted for the branded biologic without permission from the prescriber. However, laws regarding drug substitution fall within the authority of the states. Theoretically, states could pass laws that allow any biosimilar to be substituted for a corresponding branded biologic. States could also pass laws that prohibit substitution with biosimilars that have been designated as therapeutically equivalent and interchangeable by the FDA. However, it is more likely that most states will require prescriber consent for substitution of biosimilars that lack the interchangeable designation and will allow pharmacists to automatically substitute interchangeable biosimilars for branded biologics (perhaps with prescriber notification). It is also anticipated that in some states, prescriber notification requirements may apply only to community and retail pharmacy settings.

Some states have begun to consider, or have already passed, legislation regarding the dispensing of biosimilars. So far, the main focus of this legislation has been to ensure that pharmacists do not automatically substitute biosimilars; that prescribers are notified even when interchangeable biosimilars are substituted; and, in some cases, that patient consent is obtained when a biosimilar is substituted. As of September 1, 2015, bills or resolutions have been filed in 31 states, and 16 states have enacted laws regarding biologics and biosimilar substitution.

BIOSIMILAR MANUFACTURING CONSIDERATIONS

When evaluating biosimilars, it is important for P&T committee members to understand the clinical implications inherent in biosimilar production. Chemical drugs have smaller and less complex molecular structures than biologics or biosimilars. The molecular weight of chemical drugs ranges from several hundred to several thousand daltons. These products are synthesized through predictable chemical processes and can be well-characterized through analytical methods, which demonstrate that a generic version contains the identical active ingredient as a branded chemical drug. Since chemical drug molecules are small, they are usually not immunogenic unless bound to a carrier protein.

In contrast, the large molecules of biologics have weights in the range of ten thousand to several hundred thousand daltons. Rather than having a simple chemical structure, biologics are composed of glycoproteins, amino acids, and sugar molecules. Biologics manufacturing also involves numerous complex proprietary processes, such as the identification and cloning of a targeted gene sequence, use of a vector to transfer the gene into an expression system, and techniques for cell expansion, filtration, centrifugation, and purification.

The abbreviated 351k regulatory pathway is based on the concept that the manufacturing process for a biosimilar product is comparable to a manufacturing process change for a branded originator biologic. However, the manufacturing of a biosimilar

Figure 1  The Differing Complexity of Biologics and Chemical Drugs

This illustration depicts the markedly greater structural complexity of the biologic agent, erythropoietin, compared with aspirin, a conventional, small-molecule chemical drug.
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differs because development occurs without full access to the history of the branded agent, since this information is proprietary and confidential.12,17 Further, biosimilars manufacturers don’t have access to the cell line that is used to produce the branded originator biologic.12,17 Because the manufacturing and purification processes for biologics are complex, differences in the quality, safety, and efficacy of the end product can occur even when only minor alterations are made.4,12 Such alterations might include a change in the source of raw materials, temperature, pH, agitation, or contamination by chemical substances that can leach from containers and equipment.17

Because the end product is sensitive to minor changes, differences between branded originator biologics and biosimilars are unavoidable.12 The safety and efficacy of a biosimilar or biologic product may also vary over time due to manufacturing changes; this phenomenon is referred to as “drift.”6

Changes in manufacturing processes can also produce structural isomeric variants, which are impurities that influence the efficacy and safety of biologic drugs.17 Primary, secondary, tertiary, and quaternary structure, as well as the tendency to aggregate and post-translational modifications (such as oxidation, glycosylation, and phosphorylation), can affect the efficacy and safety profile of a biologic and its potential for immunogenic activity.6 An immunogenicity reaction is a major safety concern because it can cause serious clinical consequences.14,18 The potential for a biologic to produce an immunogenicity reaction varies according to the type of therapeutic protein the agent represents.4 The more similar a biologic is to a human protein, the less chance that an immunogenic reaction will occur.4

Other factors that can affect the immunogenicity of biologics and biosimilars include impurities, formulation changes (such as the removal of albumin), route of administration, dose, and immune status of the patient.4

CLINICIAN AWARENESS OF BIOSIMILARS

The acceptance and use of biosimilars will hinge on HCPs’ comfort level in prescribing and dispensing them.2 However, it appears that clinicians’ understanding of biosimilars varies.4 A study conducted in 2011 at the 16th Annual Conference of the National Comprehensive Care Network (NCCN) surveyed 277 HCPs, including pharmacists (n = 38), physicians (n = 129), and nurses (n = 71).4,18 The study found that only 13%, 8%, and 12% of these professionals, respectively, considered themselves to be “extremely familiar” with the abbreviated regulatory pathway for biosimilars, whereas 18%, 39%, and 44% considered themselves to be “not at all familiar.”4,7,19 This lack of familiarity was also demonstrated in a 2012 survey of institutional pharmacists.13 In that survey, only 44 participants (40.7%) knew that the BPCIA had granted the FDA the authority to create an expedited approval pathway for biosimilars.13

However, clinician awareness regarding biosimilars may have improved since those surveys were conducted. In a December 2014 online survey of members of the Academy of Managed Care Pharmacy (AMCP), the American Pharmacists Association (APhA), and the American Society of Health-System Pharmacists (ASHP), pharmacists were asked to rate their familiarity with biosimilars on a scale of 1 to 5, with a rating of 5 being “most familiar.”9 Over half of the respondents (66.2%, n = 93) indicated that they had a familiarity level of 4 or 5 regarding biosimilars.9 However, for interchangeable biosimilars the percentage of survey participants expressing this high degree of familiarity fell to 50.6%, indicating that knowledge gaps with respect to biosimilars still exist among pharmacists.9

P&T COMMITTEE APPROACH TO EVALUATING BIOSIMILARS

Current ASHP guidelines state that generic drugs that are considered to be bioequivalent by the FDA do not require P&T committee review.1 However, many biosimilars may not be considered by the FDA to be therapeutically equivalent and interchangeable.1 Therefore, health care systems and hospitals will need to develop policies regarding the use of biosimilars prior to formulary inclusion.1

Formulary committee best practices for reviewing biosimilars should involve proactively planning and establishing a system to evaluate these products.4 Applying sound principles for formulary management will be critical in the objective and rational evaluation of biosimilar medicines for formulary inclusion.2 The formulary review processes should include the active and direct involvement of physicians, pharmacists, and all other appropriate HCPs.4 Ethical, legal, social, educational, and quality-of-life issues should also be considered to ensure optimal patient care.4

Because of the abbreviated nature of the 351k approval pathway and the greater reliance on analytical characterization, fewer clinical data are available in comparison to branded products.2 Despite this challenge, it is expected that the P&T committee approach to evaluating biosimilars will be similar to reviewing conventional chemical drugs or branded biologics.4 Although some topics that P&T committees consider will differ, many will remain the same (Table 1).3,4 These include efficacy and safety, immunogenicity, approved and nonapproved indications, substitution and interchangeability, transition of care, pharmacovigilance, nomenclature, cost and reimbursement, HCP and patient education, and tracking- and information-system implications, among others.1–4

Table 1 Considerations for P&T Committee Members Evaluating Biosimilars for Formulary Inclusion1–4,6-12,14-17,24

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Table 2 American Society of Health-System Pharmacists (ASHP) Policy Guidelines on Approval of Biosimilar Medications

- Encourage the development of safe and effective biosimilars to make such medications more affordable and accessible.
- Encourage research on the effectiveness, safety, and interchangeability of biosimilar medications.
- Support legislation and regulations to allow FDA approvals of biosimilars.
- Support legislation and regulation to allow FDA approval of biosimilar medications that are determined to be interchangeable and may be substituted for the reference product without intervention of the prescriber.
- Oppose implementation of any state laws regarding biosimilar interchangeability prior to finalization of FDA guidance.
- Oppose any state legislation that would require a pharmacist to notify a prescriber when a biosimilar designated as interchangeable is dispensed.
- Require post-marketing surveillance for all biosimilar medications to ensure their continued safety, efficacy, purity, quality, identity, and strength.
- Advocate for adequate reimbursement for biosimilar medications that are designated as interchangeable.
- Develop and promote ASHP-directed education of pharmacists about biosimilar medications and their appropriate use within hospitals and health systems.
- Advocate and encourage pharmacist evaluation and the application of the formulary system before biosimilar medications are used in hospitals and health systems.

A discussion of these and other important considerations follows. A summary of the ASHP policy guidelines on biosimilar approval is presented in Table 2.

Clinical Considerations

Indications

Biosimilar sponsors are most often expected to pursue a subset of the indications, routes of administration, and dosage forms that have been approved for the reference product. The FDA has stated, “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.”

Therefore, the indications for an approved biosimilar may not necessarily include all of the approved uses for the corresponding branded biologic; the indications may vary depending on the sponsor’s application and whether clinical trial information supports extrapolation across multiple indications. If a branded biologic is currently used for multiple indications within a health system, it will be important for P&T committee members to define whether the biosimilar is being evaluated for all uses of the reference product—both approved indications and off-label standard-of-care uses. If an institution is using a branded biologic for off-label purposes, the P&T committee will need to consider what indications or usage restrictions it will approve for the biosimilar. P&T committees will have to make decisions based on a case-by-case evaluation of whether the mechanism of action and clinical evidence also support the use of the biosimilar product outside of the labeled indications.

Evaluation of Efficacy and Safety Using Available Data

An objective review of the scientific evidence and the medical literature should remain the foundation of the P&T committee’s evaluation process for biosimilars. However, biosimilars will require more extensive evaluation than small-molecule generic chemical drugs, and the type and amount of clinical data available will vary case by case.

The FDA has defined the types of data that will be required from manufacturers to demonstrate biosimilarity and interchangeability. The FDA regulations for biosimilar approval state that in vitro and in vivo functional assays should provide evidence that the activity and potency of the biosimilar are highly similar to the reference product, and/or support the conclusion that there are no clinically meaningful differences between the biosimilar and the reference product. They also state that studies assessing the immunogenicity and pharmacokinetics or pharmacodynamics of a biosimilar should be designed “to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed.” However, there are unique considerations with regard to evaluating biosimilar clinical studies. According to FDA regulations, the nature and scope of the clinical studies required will depend on the nature and extent of residual uncertainty about biosimilarity after conducting functional and structural characterizations and, where relevant, animal studies. As a result, clinical studies submitted for biosimilar approval may often be limited.

P&T committee members will therefore need to evaluate the amount and quality of available clinical data that supported the FDA’s approval of the biosimilar, particularly for the indications under consideration for formulary inclusion. Clinical data from international sources that supported registration of the biosimilar outside the U.S., as well as international post-approval data, should also be reviewed. Any differences between the biosimilar and the branded biologic in safety, efficacy, product-specific characteristics, compatibility, or need for dosage regimen adjustments (based on renal or hepatic clearance data) should be assessed in terms of how the biosimilar will be used in the specific patient populations. Available pre- and post-approval clinical data should also be evaluated for differences in immunogenic profiles for a branded biologic and its biosimilars, evidenced by infusion reactions, neutralizing antibodies, or loss of efficacy. Pharmacists can also analyze and critique the product prescribing information and complete their own safety assessment.

The validity of extrapolating data from the branded biologic to the biosimilar will require careful evaluation, especially for immunogenicity data. When available, data from crossover studies in which patients switch from the branded biologic...
to a biosimilar or vice versa are particularly useful for demonstrating a biosimilar’s safety.3 Interestingly, a review of the medical literature for human growth hormone, erythropoiesis-stimulating agents, and granulocyte-colony stimulating factor biosimilars approved for use in the European Union revealed no safety issues when changing products, including switching between branded products within the same product class and switching to and from biosimilars.1

Irrespective of the need for clinical data, the fact that the regulatory pathway for biosimilars focuses heavily on analytical data might present a challenge for P&T committee members, who normally rely on evidence from randomized controlled trials and meta-analyses, or systematic literature reviews, as the foundation for drug evaluation.4,15 Therefore, P&T committees may need to acquire more expertise in the laboratory methods and analytical techniques that are used for evaluating biosimilars.15

Special Safety Considerations: Immunogenicity

The potential for immunogenicity reactions, especially when switching between an innovator biologic and a biosimilar, are of particular concern because they are potentially serious and even life-threatening.7 Immune-system disorders and infections are the most common safety problems associated with biologics.7 Because of their molecular size and complexity, biologics are “visible” to the immune system.1 As a consequence, they can potentially induce a range of immunological responses, some which can cause infusion reactions, anaphylaxis, or loss of product efficacy.1 Loss of product efficacy typically occurs quickly and persists because of the formation of neutralizing antibodies.7 Increasing the dose of a biosimilar may partly overcome a loss in efficacy.7 Breakdown of immune tolerance is slow to develop and less common.7 This may develop after administration of recombinant human proteins due to the presence of impurities or protein aggregates that cause binding antibodies to form.7 These binding antibodies may disappear during or after discontinuation of treatment.7

Various product- and patient-related factors contribute to the immunogenicity of biologics.7 Product-related factors include structural (e.g., amino acid sequence, glycosylation) or formulation properties and the presence of impurities or contaminants (e.g., protein aggregates due to improper processing, storage, or handling).7 Patient-related factors include the duration and route of administration, immune status, and genetic background.7 Regarding treatment duration, a high frequency of immunogenicity is observed with longer periods of administration of biologics.7 Intramuscular and subcutaneous injections are more immunogenic than intravenous injections, and topical administration is the least immunogenic route.7 With respect to immune status, immunogenicity reactions occur less frequently in immunocompromised patients than in immunocompetent patients as a result of impaired antibody formation.7

Unfortunately, the immunogenicity of biologics is difficult to predict because of the limitations of available immunogenicity assays.7 However, immune reactions to biologics, such as allergy, anaphylaxis, and serum sickness, are becoming more rare due to improvements in the purity of biologic drugs.7

Product Considerations

Nomenclature

Although not yet officially decided, the naming convention for biosimilars will be important for pharmacists, physicians, and payers.4,7 For the sake of simplicity, most stakeholders would like to see biosimilars identified by a generic name that corresponds with the branded biologic.4,20 However, unlike conventional generic chemical drugs, biosimilars differ structurally from the branded biologics; therefore, they may not automatically be assigned the same generic name.8 Multiple biosimilars for each branded biologic agent may also be available, so it would not be appropriate for all of them to be known by the same generic name because each will have unique characteristics due to manufacturing considerations.8 Assigning all related biosimilars the same generic name would also complicate prescribing and dispensing of these agents and would complicate reimbursement and post-marketing tracking.3–6,21

A unique but simple naming system for biosimilars would provide many advantages.4 In the U.S., generic names are approved through the U.S. Adopted Names Council (USANC), which is sponsored by the American Medical Association, the United States Pharmacopeial Convention, and the APhA.3 USANC selects simple, informative, and unique generic names for drugs based on logical nomenclature classifications associated with pharmacological and/or chemical relationships.1,12 USANC has had an increasingly prominent role in developing naming rules and assigning names for biologic agents.5 The FDA is represented in USANC, so it collaborates in the selection of generic names.9 In August 2015, the FDA issued draft guidance proposing that the generic biologic name be followed by different suffixes to identify branded biologics and biosimilars. The FDA also requested public feedback regarding whether an interchangeable biosimilar should be identified by the same suffix as its corresponding branded biologic.

Both sides of the debate regarding whether to use the same or a different generic name for branded biologics and their biosimilars have compelling arguments for their positions.9 Proponents of using the same generic name for biosimilars note that different names would cause confusion among prescribers, which might negatively affect the substitution of interchangeable biosimilars and create an artificial barrier to their adoption.6,9,15 They suggest that using National Drug Code (NDC) numbers or other product identifiers is sufficient to ensure accuracy for the purposes of substitution and post-marketing surveillance.9 However, it may be challenging to trace adverse events accurately via NDCs and lot numbers, since not all health systems use these identifiers.2 Proponents of using a unique generic name for biosimilars cite the need to reduce inappropriate or inadvertent product switching, as well as to clearly identify products for the purposes of substitution, pharmacovigilance, and patient surveillance.2,7,9 However, the use of unique nonproprietary names for biosimilars may also have disadvantages, including confusion among prescribers about the comparability and interchangeability of products, as well as prescribing and administration errors.7

Participants in the 2014 online survey of AMCP, APhA, and ASHP members were asked how confident they would be in substituting interchangeable biologics under different naming scenarios.9 The results indicated that the majority (74.6%) of
pharmacists felt “confident” or “very confident” in substituting a biosimilar for a branded biologic if the products shared the same nonproprietary name. When presented with a scenario in which the biosimilar and the branded biologic had different nonproprietary names, only 25.3% of participants indicated they had the same confidence level. The results of this survey indicate that the naming convention selected for biosimilars will play a role in substitution practices for interchangeable biosimilars, since a majority of pharmacists in this survey indicated feeling “confident” or “very confident” only when an interchangeable biosimilar and branded biologic share the same generic name.

Regarding the review of biosimilars for formulary inclusion, P&T committee members should consider how biosimilar names will affect institutional computer systems used for tracking adverse events associated with a dispensed biologic or biosimilar. The use of distinct names for biosimilars and branded biologics is one of several ways pharmacists will be able to track these products; however, it may be necessary to implement special procedures if these agents share the same generic name. The use of NDC data or bedside bar-code scanning may alleviate concerns regarding drug tracking because this information can be entered into an electronic medication administration system, but this technology may not be available to all HCPs.

### Manufacturer and Supply Chain Considerations

As patents for branded biologics expire, many originator molecules are being targeted for biosimilar development. Unlike the current industry scenario in which pharmaceutical manufacturers primarily make either branded or generic products, a blended array of companies is expected to participate in producing biosimilars. Manufacturers traditionally thought of as “generics companies,” such as Hospira, Sandoz, and Teva, are expected to compete with originator companies such as Genentech in bringing biosimilar products to market. Other brand-name companies, such as Amgen, Merck, and Pfizer, are also expected to develop versions of competing originator companies’ branded biologics. Collaborations between generics and brand-name manufacturers for the purpose of participating in the biosimilar market have also been announced.

When reviewing biosimilars for potential formulary inclusion, it is important to evaluate manufacturer and supply chain considerations. Since switching between different versions of biologic medications can potentially cause an immunogenicity reaction, it is important to have a reliable and consistent supply of medication. Therefore, P&T committee members should consider whether a manufacturer has a process to ensure a reliable and uninterrupted product supply and whether adequate stock is produced and stored to fulfill demand. P&T committee members should also consider whether a manufacturer has backup or multisite manufacturing capabilities, as well as its history of product shortages and recalls. Shortages due to quality issues such as particulates and contamination can indicate ineffective quality control processes and difficulty in maintaining a quality drug supply. Handling practices for products should also be evaluated, including manufacturer documentation of controlled temperature during distribution and steps taken to prevent contamination of product vial exteriors.

Supply chain security and anticounterfeit protection are also important factors for P&T committee members to review when evaluating biosimilars. A key question regarding security is whether the manufacturer can document a high level of protection against supply chain interference by illegal drug diversion or counterfeiting. Such measures may include security systems and procedures at the warehouse, carrier, truck, and pallet level; market surveillance to monitor for product diversions and to detect counterfeits; and forensic security technologies for product authentication.

### Packaging, Labeling, and Storage

P&T committee members should consider whether product labeling and packaging are clear enough to allow differentiation between a biosimilar and branded biologic. Product labels and packaging should be clear and easy to read, and product containers and delivery devices should be well designed for use by both HCPs and patients. Pharmacists should also consider differences in shelf life, storage temperature, light sensitivity, and routes of administration that could compromise product integrity or patient safety. It is also important for pharmacists to consider whether a branded biologic and its biosimilar will both be stocked, and, if so, how they will be stored to reduce the risk of dispensing errors. P&T committee members should also consider the time and techniques that may be required for a biosimilar compared to a branded biologic, with respect to the institution’s compounding technologies and practices.

### Institutional Considerations

#### Substitutions and Interchangeability

The distinction between biosimilars with and without an interchangeable designation is important for pharmacists, especially when it comes to formulary decisions. Although state laws may differ, FDA regulations permit interchangeable biosimilars to be substituted for a branded biologic without notifying the prescriber. The BPCIA included more rigorous requirements for designating a biosimilar as interchangeable. The FDA’s interchangeable designation requires that a biosimilar “can be expected to produce the same clinical result as the reference product in any given patient.” It also requires that when a biosimilar is “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.” The distinction between biosimilars with and without an interchangeable designation may limit the role of these agents, as well as the flexibility that institutions and health plans may have in formulary design and utilization management.

Routine generic drug substitution practices cannot automatically be applied to all biosimilars because some will lack an interchangeable designation, so these agents present unique opportunities and responsibilities for P&T committees. As committee members review biosimilars for formulary inclusion, they will need to consider whether a biosimilar has been designated as interchangeable by the FDA and, if so, whether this applies to all or only certain indications. Since not all biosimilars will have an interchangeable designation, this means...
substitution must be evaluated by the P&T committee on a drug-by-drug basis and verified in a national compendium. The FDA has announced that it will publish a “Purple Book,” which will list all approved biosimilars and will note whether they have been granted an interchangeable designation with a specific branded biologic. In addition, P&T committees need to investigate and take into account state laws regarding the substitution of biosimilars as they develop institutional policies and procedures.

**Therapeutic Interchange**

Even if state law or the FDA does not permit a biosimilar to be automatically substituted for a branded biologic, health systems may still consider the use of therapeutic interchange. This powerful tool authorizes the exchange of therapeutic alternatives that have been deemed therapeutically equivalent, according to approved written protocols and guidelines within a formulary. Therapeutic interchange differs from interchangeability in that it is the dispensing of a drug that is therapeutically equivalent to the prescribed drug but is chemically different. Biosimilars must have the same mechanism of action as the branded biologic and highly similar pharmacokinetics and toxicities to be considered interchangeable, whereas drugs used in therapeutic interchange can differ in these respects. Therapeutic interchange is often permitted to simplify the formulary and improve purchasing contracts to lower overall costs. It is likely that health systems will use therapeutic interchange to consolidate the use of biosimilar agents within their formularies.

When considering therapeutic interchange for a biosimilar that lacks an interchangeable designation, P&T committee members will need to conduct a thorough risk–benefit evaluation. An objective evaluation of whether the use of a biosimilar should be permitted in therapeutic interchange can be conducted by applying formulary process and therapeutic interchange guidelines and protocols. This involves asking questions about:

- Therapeutic and dose equivalence, efficacy, and safety risks when switching products.
- Cost advantages of one product over another.
- The potential for a clear interchange process and understanding by prescribers.
- The ability to opt out in specific circumstances.
- The ability to monitor and assess efficacy and safety outcomes.

A formulary committee could also decide to allow therapeutic interchange only for patients who have not previously been given the branded biologic. However, this approach may be inconvenient, since it would require maintaining separate stocks, creating procedures to prevent inadvertent switching, and establishing clear direction regarding how prescribers would write orders for these patients.

**Transition of Care**

It is also important for P&T committee members to consider the implications of policies and practices for patients affected by transition of care issues. Payers will likely provide incentives for the use of biosimilar medicines to reduce or control costs. This could include substantially higher copayments or coinsurance premiums for use of the originator product when a biosimilar medicine is available. However, branded biologic manufacturers could also offer contracts to health systems that provide significant discounts to encourage the continued use of an originator product when biosimilars are available. This will create a dilemma regarding whether to sacrifice discounts on the branded biologic in order to reduce switching to a biosimilar at the transition of care, which will ensure that the patient experiences minimal financial impact relating to drug costs.

Frequent switching between a biosimilar and branded biologic may also cause variable efficacy and safety outcomes, making causality difficult to assign. The efficacy and safety of a biosimilar or branded biologic may also drift over time due to manufacturing changes, providing another reason to avoid unnecessary switching at transition of care.

**Pharmacovigilance**

Pharmacovigilance programs are necessary to determine whether the safety profile of a biosimilar is comparable to that of its branded biologic. Pharmacovigilance will be critical to tracking immunogenicity reactions and other unforeseen adverse events that may occur with biosimilar use.

Because the biosimilar regulatory pathway is abbreviated, the number of subjects enrolled in required clinical studies is likely to be smaller than the number required for the approval of an originator biologic. A small study that enrolls a population of a few hundred patients is sufficient to demonstrate comparability; however, this is an inadequate sample size to thoroughly assess the adverse-event profile and immunogenicity. In addition, the time horizon for biosimilar clinical studies is not expected to be long enough to reveal all potential adverse events.

Therefore, post-marketing surveillance is necessary to supplement the clinical trials that are required by the FDA for biosimilar approval. Health systems must ensure that a pharmacovigilance program is in place to accurately track adverse events associated with biosimilar products. Ideally, in addition to monitoring the efficacy and safety of biosimilars for approved indications in standard populations, post-marketing surveillance will be helpful for monitoring diverse patient populations and off-label uses. The need for pharmacovigilance is magnified when biosimilars from multiple sources are used, since slight product differences may cause clinically important effects.

Post-marketing surveillance can be accomplished by many means, including the implementation of patient registries and prospective or retrospective observational and epidemiological studies. However, prospective patient registries are complex, cumbersome, and costly to implement. Establishing electronic health records may assist pharmacovigilance efforts regarding biosimilars. Data mining is less burdensome because it relies on routinely collected data; however, it is not proactive. The use of standardized risk evaluation and mitigation strategies is likely to be the most cost-effective strategy for health systems to use for pharma-
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covigilance because it optimizes efficiency while fulfilling FDA requirements.7
Pharmacists can support product safety monitoring by promoting the maintenance of accurate medical records (including documenting lot numbers at the time of administration) for biosimilar therapies, as well as by working with physicians on forensic evaluations of adverse drug reactions.2 Pharmacists can also contribute to post-marketing surveillance efforts by submitting MedWatch reports to the FDA.3 Whatever the approach to facilitating pharmacovigilance efforts, biosimilar agents will also need to be identified with unique nonproprietary names and NDC or billing codes in accounting records and/or in electronic health records so that they can be traced; this capability may vary by setting.4

Cost
Biosimilars are expected to substantially reduce drug expenditures in hospitals and health systems, assuming that they achieve the same clinical results as branded agents.3,13,25,28 However, some experts speculate that biosimilars will not provide the same magnitude of cost-savings on a percentage basis that generic chemical drugs offer compared with branded products.1,5,7 In the U.S., differences of up to 80% in price between generic and branded chemical drugs have been observed.12,14 However, because biosimilars require much higher research and development costs, it is expected that they will be discounted by only 15% to 35% compared with corresponding branded biologic agents.1,3,5,7,14,18,25

Considering the high cost of biologics in the U.S., a savings of 15% to 35%—although not as dramatic as the savings provided by generic chemical drugs—is still substantial in terms of the dollar amount.1,3 A treatment course of a branded biologic product can cost tens of thousands of dollars per patient, so a 20% discount on the billions spent on biologics each year ($100 billion in 2010) is significant and is expected to increase access and affordability for patients.2 Decreased spending on branded biologics will also generate significant savings for federal Medicare and Medicaid programs, assuming that biosimilars produce the same clinical results.1,15 Additional cost-savings are expected to occur as biosimilars gain market share, causing prices to decline further.12,14

Cost-savings are an important factor for P&T committees to consider when evaluating biosimilars.5 There will no doubt be significant opportunities for cost-savings; however, formulary decisions must be executed in a way that protects clinical outcomes. They should be evidence-based rather than primarily focused on economics.1,4,17 The economic impact of biosimilars should also be considered from the point of view of the institution, payer, and patient during formulary review.2 Rather than solely considering acquisition costs, P&T committees should consider the total cost of using any drug, whether a biosimilar or branded biologic.2 It will be important to understand whether the difference in total cost between biosimilars and branded biologics will support a full formulary conversion to the biosimilar.2 Group purchasing organizations (GPOs) will also need to develop strategies that create the right balance between patient safety, best price, and minimal switching due to new contracts.8

The financial considerations taken into account by P&T committees should include:2,4

• Financial impact on the health care system.
• Inpatient costs of administration.
• Costs for patient and institutional support programs.
• Medical information support.
• Costs for technology changes.
• Costs for pharmacovigilance.
• Costs associated with drug shortages.
• Outpatient margin.
• Costs for monitoring the response to biosimilar treatment.
• Potential additional monitoring costs when there is therapeutic interchange.
• Influence of bundled contracting approaches on cost.
• Influence of patient-assistance programs on cost.
• Out-of-pocket costs for patients and potential impact on access and adherence.

After biosimilars are added to the formulary, it is expected that most agents will need to be vetted through a cost-control method such as prior authorization or managed care pharmacy step-edit processes.13 P&T committees will have sufficient financial incentive to integrate biosimilars into drug formularies as long as adequate relative efficacy and safety data are available.3,12 If appropriately designed and powered clinical studies have demonstrated equivalent efficacy between a biosimilar and a branded agent, then a cost-minimization analysis should be conducted, and the least expensive medicine will generally be chosen for the formulary.12,14 If efficacy differs, another economic evaluation will have to be conducted, such as a cost-effectiveness or cost-utility analysis.12

Savings arising from the lower price of a biosimilar will need to be weighed against differences in efficacy and the impact on total health care costs.14 The potential differences between the long-term efficacy and safety of a biosimilar and a branded agent could give rise to additional costs for health care and productivity losses, reducing the cost-effectiveness of the biosimilar agent.12 A cost-effectiveness assessment for a biosimilar should be calculated at its introduction and at multiple time points throughout the product’s life cycle, given that some uncertainty exists regarding the long-term safety and efficacy of these medications.12 Any databases or observational studies established by manufacturers to demonstrate the post-launch cost-effectiveness of a biosimilar will aid analyses.12

Reimbursement
Consideration of reimbursement and payer policies for biosimilars will be an important element of formulary reviews.2 P&T committees will need to consider cost pressures from payers to use less expensive products on the formulary, as well as coverage of these products outside the health system that may affect transitions of care.2 It will also be important to understand the differences between the branded biologic and the biosimilar with respect to payer requirements and prior authorizations.2 Payers’ reimbursement policies for biosimilars could influence patient access to these products.1,7 The out-of-pocket copayment or coinsurance costs for the patient should be considered in the context of a formulary decision.2 For example, requiring a 20% copayment for a biologic on the fourth tier and
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a 5% copayment for a biosimilar on the third tier could mean the difference between a patients’ out-of-pocket expenditure of $200 or more per month, compared with $50 per month. A recent on-line survey of 102 health plans showed that 49% of respondents plan to place biosimilars on a lower cost-sharing tier than branded specialty drugs. 

Cost differences between biosimilars and branded biologics should also be evaluated carefully with respect to differences in manufacturer assistance programs. Although the PPACA currently caps patients’ total out-of-pocket spending at $6,600 for individuals and $13,200 for families, some patients will remain price sensitive. Manufacturer assistance programs can subsidize copayments and coinsurance, blunting the impact of differential cost-sharing. Health systems and hospitals may prefer not to switch to a biosimilar if the manufacturer does not provide a patient assistance program similar to that for the branded biologic.

When there are multiple therapies with clinically insignificant differences in efficacy and safety, health plans and pharmacy benefit managers will often exclude the more costly agents from their formularies or require patients to try an inexpensive product first (a step edit). The online survey of 102 health plans indicated that 64% of those surveyed envision implementing step edits for the use of biosimilars prior to branded products. Manufacturers of branded biologics may also provide payers with a discount or rebate program to prevent being placed in a high formulary tier. A branded biologic manufacturer could also reduce the price of an agent to discourage buyers from switching to a corresponding biosimilar. Payers could also deny reimbursement for a biosimilar administered for an off-label indication because of the lack of supporting data. Formal FDA regulations regarding the off-label use of biosimilars would help health plans and pharmacy benefit managers determine how to approach indications for which the branded biologic, but not the biosimilar, has been approved.

Because of the potential for immunogenicity reactions, pharmacy benefit managers and payers will also need to evaluate the immunogenic potential caused by switching and to consider “grandfathering” in patients who have already begun treatment with a branded biologic. Under such a policy, any patient who has previously received the branded biologic would be permitted to continue with the drug, despite a formulary exclusion or step edit. Under such circumstances, patient cost-sharing might also be relaxed, since the patient initiated treatment with the branded agent before a biosimilar was available.

Provider and Patient Education

In addition to formulary management, hospitals and health systems must address educational needs regarding biosimilars. Three areas should be emphasized for pharmacists: 1) the substitution and interchangeability of biosimilars; 2) pharmacovigilance programs; and 3) notification requirements required by state laws when a biosimilar is substituted. Pharmacists and other HCPs should also understand comparability exercises, potential risks, and naming conventions associated with biosimilars. Health-system pharmacists can play an important role in educating administrators, physicians, other HCPs, legislators, policy-makers, payers, and patients about the FDA approval process, differences between innovator biologics and biosimilars, and the need for post-marketing pharmacovigilance. The ASHP Advantage website (www.ashpadvantage.com) provides a good resource for educational activities (including continuing medical education) and information regarding biosimilars. Pharmacists may also wish to contact professional and business organizations such as the NCCN and GPOs that may provide educational materials concerning biosimilars.

Patients are generally familiar with the concept of generic medications; however, they will need to be educated about biosimilars. Patients should be advised about the pros and cons of being prescribed or switched to a biosimilar. For biosimilar products that are self-injected, patients should be alerted that the pre-filled syringe will likely differ from that of the branded biologic. HCPs should be involved in informing patients rather than solely relying on materials distributed by pharmaceutical manufacturers. Pharmacists, physicians, and nurses will need access to patient-appropriate drug information to address the numerous questions that patients will likely have. As a part of the P&T committee’s evaluation of biosimilars for formulary inclusion, patient education materials provided by the manufacturer should be reviewed. If appropriate patient education materials are not available, the P&T committee should consider developing materials to educate patients on important topics, such as proper use, interchangeability, and transition of care.

Information Technology

Regardless of the naming convention that is ultimately followed, P&T committee members will need to evaluate operational information technology systems that will be necessary to accurately manage and track biosimilars. Pharmacists should ensure that the hospital information technology system is capable of distinguishing between originator biologics and biosimilars and can accurately track the specific drug(s) a patient receives. Health systems must ensure that the capability for distinguishing biosimilars from originator biologics (and from each other) exists throughout the medication-management continuum, including the electronic medical record, electronic medication administration profiles, the order-entry interface, predefined order sets, care paths, bedside bar-coding, and protocols through final product labeling. Inventory management systems (including automated dispensing devices and associated software) and purchasing systems must also allow the accurate identification of biosimilars by pharmacy buyers, technicians, and anyone else involved in the pharmacy supply chain.

CONCLUSION

Biosimilars will provide a tangible opportunity for health care organizations to manage the growth of pharmaceutical expenditures. P&T committee members will play a leadership role in adopting and using biosimilars appropriately through applying formulary and practice management tools and principles. However, because of the variety and complexity of biosimilars, an especially in-depth analysis will be required when evaluating biosimilars for formulary inclusion. In addition to standard considerations, many other regulatory, manufacturer, clinical, product, and institutional concerns will have to be evaluated during the formulary review. P&T committee members will also need to assess patient considerations, including cost/
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reimbursement, substitution/interchangeability, transition of care concerns, and patient education. To ensure the safe and effective use of biosimilars, P&T committee members should lead the effort to educate HCPs, patients, payers, and other stakeholders about these agents.

REFERENCES