Biologic, Biosimilar, and Interchangeable Biologic Drug Products

Background Paper Prepared for the 2015–2016 APhA Policy Committee
Edward Li, PharmD, MPH, BCOP
Associate Professor
University of New England College of Pharmacy

Issue

The American Pharmacists Association (APhA) Board of Trustees has directed the 2015–2016 Policy Committee to recommend policy to the APhA House of Delegates. The Board’s guidance on this topic included, but was not limited to, product interchangeability, product naming conventions, clarification on drug development and approval, and the pharmacist’s role regarding product substitution.

Summary of Key Concepts

- Before enactment of the Patient Protection and Affordable Care Act (PPACA), a legal pathway for manufacturers to produce versions of previously approved biologic products did not exist. Since then, the Biologics Price Competition and Innovation Act (BPCIA) has created a legal pathway for this process and relies on regulation by the Food and Drug Administration (FDA) to determine the specific pathway for approval of products.
- Biosimilars are not simply generic biologics as Differences exist between scientific construction of the products themselves and approval pathways from a regulatory perspective.
- Small-molecule drugs differ from biologics in size, structure, manufacturing processes, and immunogenicity, leading to difficulty in modeling exact creation and approval processes from brand and generic processes.
- FDA has outlined a stepwise approach to obtaining approval for biosimilarity that involves studies and data of structure, function, animal toxicity, pharmacokinetics (PK) and pharmacodynamics (PD), immunogenicity, and clinical safety and efficacy. A difference with biosimilars regarding the PK and PD aspects of the end product will be a focus of final product information.
- Interchangeability remains an issue in the pharmacy profession because current federal law does not allow pharmacists to substitute these products automatically and because many states are adding varying rules or statutes regarding permission for a pharmacist to substitute these products.
- The naming of biosimilar products is still problematic despite guidance documents provided by the World Health Organization (WHO) and FDA.
- Product substitution by pharmacists is an area of further evaluation. Although FDA has created the Purple Book for assistance with biosimilar product substitution, many states are passing state-specific laws. These laws outline multiple aspects of the substitution process, including communication with providers and recordkeeping requirements.

Introduction

For most of the past two decades, some biological products have had market exclusivity in the United States. Biosimilars, approved through their own FDA pathway, introduce competition into the marketplace for biological medications. Such competition should result in more competitive (i.e., lower) prices and provide an incentive for biological product manufacturers to innovate and discover newer, more effective products. Before passage of the PPACA in 2010, a legal pathway to allow other manufacturers to produce versions of already-licensed biological products did not exist. The PPACA
included the BPCIA, which created a legal pathway for the development of biosimilars and charged FDA with developing the pathway for approval of biosimilar products.\textsuperscript{3} Table 1 describes the types of biological products (from a regulatory perspective) that can be approved by FDA. FDA licenses novel biologics through the 351(a) pathway (found at section 351[a] of the Public Health Service [PHS] Act). For novel biologics, sponsors must demonstrate safety and efficacy for market authorization. In contrast, biosimilars are approved under the 351(k) pathway. Under section 351(k) of the PHS Act, sponsors must demonstrate that the biosimilar is “highly similar” to a reference product that was approved through section 351(a) of the PHS Act. If a biologic product manufacturer decides to produce another version of an already-approved biologic product, the decision to seek approval through the 351(a) or 351(k) pathway will depend on the company’s business strategy.

### Table 1. Regulatory Types of Biological Products

<table>
<thead>
<tr>
<th>Aspect</th>
<th>351(a) Originator</th>
<th>351(k) Biosimilar</th>
<th>351(k) Interchangeable biosimilar</th>
<th>351(a) Nonoriginator biologic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>First-to market biologic molecule; will likely be the reference product</td>
<td>“Highly similar” to reference product; approved via biosimilars pathway</td>
<td>A biosimilar that meets additional standards so that it can be substituted for the reference product without permission from prescriber</td>
<td>another brand name of an already approved biologic</td>
</tr>
<tr>
<td><strong>Depth of data submitted to FDA</strong></td>
<td>Standard data package of efficacy and safety</td>
<td>Abbreviated data package for comparability</td>
<td>Abbreviated data package for comparability; more information on switching</td>
<td>Standard data package of efficacy and safety</td>
</tr>
<tr>
<td><strong>Compared to originator?</strong></td>
<td>NA</td>
<td>Yes</td>
<td>Yes</td>
<td>Not necessary (yes or no)</td>
</tr>
<tr>
<td><strong>Implications</strong></td>
<td></td>
<td></td>
<td>Biosimilar pricing; explicit regulatory oversight on comparison with reference product; possible product substitution by pharmacist (for interchangeable biosimilars)</td>
<td>Different pricing structure and substitution issues</td>
</tr>
</tbody>
</table>

FDA = U.S. Food and Drug Administration; NA = not applicable. (Adapted from Lucio et al, 2013)\textsuperscript{3}

Akin to generic small-molecule drugs, biosimilars have the potential to drive down prices of biological products through competition. Patients can realize significant cost savings when pharmacists, as medically appropriate for each patient, substitute a less expensive biosimilar with an equivalent safety and efficacy profile for the branded biologic. However, significant differences exist between biosimilars and generics that add a layer of complexity to the issue of a pharmacist’s product substitution of biological medications. Generic small-molecule drugs are approved through the Abbreviated New Drug Application pathway, where the standard of approval is whether the generic drug is bioequivalent to the branded product. Thus, FDA does not require additional data regarding safety and efficacy from the generic product manufacturer. However, the bioequivalence standard alone is not sufficient in regard to allowing different versions of a biological product to come to market. Therefore, a new standard has been established to explicitly compare biological medications—biosimilarity. Biosimilars are not simply generic biologics, and the differences in scientific principles of construction and approval processes must be carefully considered in regulatory and practice contexts. The standards of bioequivalence and biosimilarity are juxtaposed in Figure 1, which compares the approval pathways for drugs and biologics. This background paper reviews the differences between biologics and small-molecule drugs and discusses how these differences translate into a distinct manner in approving for market and regulating biosimilar products. This distinction has a clear effect in the way pharmacists will practice.
Figure 1. Approval Pathways for Small-Molecule Drugs versus Biologics

Source: (Li et al., 2015)\(^5\)

**How do Biologics Differ from Small-Molecule Drugs?**

According to the U.S. Code of Federal Regulations, Section 600.3, the technical definition of a biologic is: “any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of diseases or injuries of man.”\(^6\) These are medicinal protein products derived and produced from living organisms, typically bacterial, fungal, or mammalian cells, whereas small-molecule chemical drugs are synthesized through chemical reactions within a controlled environment. Because biological medications are manufactured using living systems, they are typically far more complex than small-molecule drugs, in size, structure, manufacturing, characterization, stability, and immunogenicity (see Table 2).\(^7\)

**Table 2. Differences between Small-Molecule Drugs and Biologics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Small-molecule drugs</th>
<th>Biologics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Size</strong></td>
<td>Small; low molecular weight</td>
<td>Large; high molecular weight</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Simple, well-defined</td>
<td>Complex, heterogeneous</td>
</tr>
<tr>
<td><strong>Manufacturing</strong></td>
<td>Reproducible chemical reactions in which identical copies of the active ingredient can be made</td>
<td>Creation through living systems; impossible to fully copy active ingredient</td>
</tr>
<tr>
<td><strong>Characterization</strong></td>
<td>Completely characterized</td>
<td>Impossible to fully characterize molecular composition</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>Stable</td>
<td>Unstable; sensitive to external conditions</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Mostly nonimmunogenic</td>
<td>Immunogenic</td>
</tr>
</tbody>
</table>

Adapted from (Declerck 2012)\(^7\)

In particular, the manufacturing of biological medications differs vastly from that of small-molecule drugs.\(^8\) As protein products with a clear amino acid sequence, biologics are produced by a target DNA
(deoxyribonucleic acid) sequence being transferred into a target host cell through a vector such as a plasmid or a viral vector. After a manufacturer determines that this transfected host cell can effectively express the protein, the cells are cultured and expanded within large bioreactors under specific, controlled conditions (e.g., growth media, temperature, etc.). When the cells have produced a sufficient amount of the biologic, it must be recovered through a combination of filtration and centrifugation, and finally purified through chromatography. The structure, function, and purity of the final bulk drug must then be fully characterized using analytical techniques. Because of the inherent heterogeneity of the process, the final biological product will contain a myriad of different components, such as an active biologic with different post-translational modifications to the protein and impurities within the bulk product. However, the pattern of these components should be consistent from lot to lot and must meet specific quality standards as currently outlined by international standards discussed in many FDA guidance documents.\(^9\)

The composition of the resulting finalized biological product is highly dependent on the manufacturing process, and changes to the process may result in a different product (e.g., with post-translational modifications or impurities), which may or may not be clinically meaningful in terms of efficacy and safety (including immunogenicity). When biological product manufacturers are considering a manufacturing change, they are subject to current FDA regulations that explain which data need to be submitted to FDA to demonstrate that the potential changes will not result in any “adverse impact on the quality, safety, and efficacy of the drug product.”\(^10\) This process has been successfully applied to many biological products currently available in the United States. For example, rituximab, etanercept, and darbepoetin have undergone manufacturing process changes. Despite some differences in post-translational modifications of the product, no clinical consequences were expected and thus FDA deemed no labeling changes or further clinical studies necessary.\(^11\)

The aforementioned process is used when a manufacturer of an existing biological product desires a manufacturing change, mostly as a result of improvements in technology or increases to production scale or in response to fluctuations in the supply of raw materials. Such changes are common and can occur infrequently or upward of 30 times within a biologic’s life cycle.\(^12\) However, when another biological product manufacturer (manufacturer B) wishes to produce a version of an existing product from an originator manufacturer (manufacturer A), the manufacturing process is likely to differ significantly from the originator manufacturer’s process, because of proprietary processes and trade secrets.

Accordingly, the concerns regarding whether the final biological product is comparable from manufacturer A to manufacturer B also include whether differences would be likely to result in clinically meaningful effects. So unlike sponsors of generic drugs, who must demonstrate only bioequivalence, sponsors of candidate versions must show biosimilarity, meaning that the products are “highly similar with no clinically meaningful differences” (notwithstanding minor differences in inactive components). At the same time, the pathway for approval must be significantly abbreviated so that development costs for biosimilars will be lower than for novel biologics. To evaluate the safety and efficacy of biosimilars before approval, FDA has developed the 351(k) pathway noted earlier.

**FDA Guidance for the Approval of Biosimilars**

The approval of a biosimilar product is a scientifically based, comprehensive comparability exercise. The purpose for demonstrating biosimilarity is not to demonstrate that the biologic is safe and effective per se; the reference biologic’s manufacturer already demonstrated this in the initial 351(a) application to FDA. Rather, as discussed earlier, sponsors must demonstrate that the biosimilar does not have any “clinically meaningful differences,”—in essence, that it produces patient results similar to those of the reference product. Accordingly, smaller-scale studies and extrapolation are used to determine biosimilarity. FDA has outlined a stepwise approach, which includes a comparison of the candidate biosimilar to the reference biologic in the domains of structure, function, animal toxicity studies, human PK and PD
studies, clinical immunogenicity, and other clinical studies to compare efficacy and safety. As depicted in Figure 2, this stepwise approach compares the biosimilar to the reference biologic in physiochemical and biological characteristics (through in vitro methods) and bioequivalence (all biosimilars must be bioequivalent to the reference product), safety, and efficacy through human clinical trials.

Figure 2. The Stepwise Development Approach for a Biosimilar

PK = pharmacokinetics; PD = pharmacodynamics. Adapted from (Li et al. 2015)

Table 3 outlines the elements within each step to address comparability of the candidate biosimilar to the reference biologic within each domain. In each of the clinical studies, the endpoint chosen for comparison between the reference biologic and the biosimilar will be the most sensitive—where differences in the endpoint would translate into clinical differences between the products. The data package for biosimilars represents a paradigm shift from the way clinicians are accustomed to making therapeutic decisions. For biosimilars, the data package will focus more on the preclinical analyses of structure and function with robust evidence for PK and PD and less on comparative clinical studies for efficacy. Accordingly, FDA may choose to use a clinical study evaluating one indication and extrapolate the approval of the biosimilar to include some or all of the reference product’s FDA-approved indications. The extrapolation decision is based on many factors such as the similarity of the mechanism of action across extrapolated indications, the target receptors involved, the immunogenicity profile between extrapolated populations, and the extent of the preclinical data.

Table 3. Stepwise Approach toward Demonstrating Biosimilarity

<table>
<thead>
<tr>
<th>Step</th>
<th>Role</th>
<th>Element</th>
</tr>
</thead>
</table>
| **Structure** | Serves as the foundation for biosimilar development | • Determine quality attributes in terms of amino acid sequence, higher-order structures, post-translational modifications (e.g., glycosylation, PEGylation), etc.  
• Analyze lot-to-lot variability. |
| **Function** | Serves as the foundation for biosimilar development | • Determine quality attributes in terms of pharmacologic activity through in vitro or in vivo experiments.  
• Determine specific assays based on the molecule’s mechanism of action. |
<table>
<thead>
<tr>
<th>Animal toxicity</th>
<th>Useful when unresolved questions exist about the safety of the candidate biosimilar based on studies of structure and function</th>
<th>• Comparative animal toxicology design depends on the unresolved questions identified through comparability studies of structure and function.</th>
</tr>
</thead>
</table>
| Pharmacokinetics (PK) and Pharmacodynamics (PD) | Fundamental for demonstrating biosimilarity | • Assess bioequivalence in a sensitive population (PK).  
- Use a sensitive PD endpoint that is predictive of clinical outcomes.  
- Use crossover and parallel designs. |
| Immunogenicity | Evaluation of potential differences in incidence and severity of immune responses | • Endpoints include antibody formation (binding, neutralizing), cytokine levels, etc.  
- Comparative parallel study can be used.  
- Analysis is done mainly within the PK and PD and the efficacy and safety studies. |
| Clinical safety and efficacy | Required to answer unresolved questions based on PK and PD studies to demonstrate neither decreased nor increased activity (sometimes not necessary if there is a robust PD marker) | • Noninferiority and equivalence study designs are used.  
- Specific clinical trial design will depend on remaining residual questions.  
- Specific endpoint and population will depend on discussions with opinion leaders and with FDA.  
- FDA may be allowed to extrapolate to other FDA-approved indications. |

FDA considers the totality of the evidence when reviewing candidate biosimilars for approval. For example, if the studies of structure and function with the biosimilar are highly comparable to the reference product, then the product has very high confidence and low residual uncertainty, requiring only more targeted clinical studies to confirm biosimilarity. Likewise, if higher uncertainty exists after review of the data for structure and function, FDA may require more clinical studies, such as comparative PK and PD and safety and efficacy studies, before approving the candidate biosimilar.\(^1\) In cases involving an excellent PD marker that correlates well with clinical efficacy, the regulatory authority may not require comparative studies of efficacy and safety for approval as a biosimilar.\(^1\) Immunogenicity assessments will be incorporated into the human clinical studies and are required to be comparable in incidence and severity of immune-related effects.

Although FDA has not yet created a pathway for determinations of interchangeability, biosimilars demonstrating that switching between the reference product and the biosimilar in the same patient creates no immunogenic and other safety concerns may be designated interchangeable with the reference product. The implications of being an interchangeable biosimilar are discussed later.

Because clinical studies for market approval are not designed to detect rare but serious adverse events, long-term pharmacovigilance studies are also important for ensuring that a biosimilar is equivalent to the reference biologic in safety events. One of the main goals with ongoing pharmacovigilance programs is assessing whether serious adverse events (should they arise) are product specific (e.g., a result of the
vehicle or other factors of the final biological product) or molecule specific (e.g., a result of the molecule’s pharmacologic properties).

**Unresolved Policy Issues**

The FDA has finalized its guidance documents for industry and has approved the first biosimilar in the United States. However, a number of issues have not been resolved at the national level: interchangeability, biosimilar naming, and Medicare and Medicaid reimbursement.

**Interchangeability**

Provisions within the BPCIA allow for a biosimilar to be designated *interchangeable* if it meets additional standards beyond biosimilarity. An interchangeable product is one that “can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch.” Currently, FDA has not released guidance regarding what data are required from a biosimilar product manufacturer to meet the definition of interchangeability. However, statisticians have proposed various study designs that incorporate switching between the biosimilar and reference product.

The implications for the availability of an interchangeable biosimilar product are clear: the BPCIA indicates that interchangeable biosimilars “may be substituted for the reference product without the intervention of the prescribing healthcare provider.” The fact that the BPCIA does not give pharmacists the authority to make substitutions is important; pharmacists practice under the authority given to them by individual state pharmacy practice laws. However, because FDA has not yet released interchangeability standards and because current guidance documents indicate that FDA anticipates that obtaining an interchangeability designation at the time of first approval will be “difficult,” interchangeable biosimilars are unlikely to be available in the near future. Further, if sponsors of biosimilars approved before the development of an interchangeability pathway want to switch their product designation to interchangeable, they will almost certainly have to submit additional clinical and other supporting data (note: a product can be a biosimilar or an interchangeable biosimilar, but not both).

**Biosimilar Naming**

The nonproprietary naming of biosimilars has been another area of contention since the passage of the BPCIA. The issue has two sides: whether the biosimilar should share the reference product’s exact nonproprietary name, or whether biosimilars should have distinct names. Those who advocate for the same name cite the experience with generic drugs that the same name facilitates substitution and may improve public and prescriber acceptance and uptake of biosimilars. In a recent survey of pharmacists who are members of the Academy of Managed Care Pharmacy, American Society of Health-System Pharmacists, or APhA, respondents indicated greater confidence in substituting an interchangeable biosimilar for the reference product if both products shared the same name. Advocates for different names state that such names are necessary to facilitate pharmacovigilance programs. Currently, both active and passive adverse event surveillance programs identify products through their nonproprietary names. Limitations have been identified where having the same nonproprietary name may lead to false safety signals. In one study, the authors identified an underrepresentation of reports that were specifically attributable to a generic enoxaparin manufacturer when evaluating spontaneous reports to the FDA MedWatch program, despite a robust market share of generic enoxaparin products. Proponents of a shared nonproprietary name counter the pharmacovigilance argument by suggesting that deficiencies in
reporting systems should be addressed by improving those systems rather than proceeding through the biosimilars naming framework.

Recently, the World Health Organization released its proposal to address biosimilar naming. It suggests adding a voluntary, four-character \textit{biological qualifier} to the end of the biologic’s traditional international nonproprietary name (INN), not as part of the INN, but as an “additional and independent element used in conjunction with the INN.” This biological qualifier would be devoid of meaning, but it would allow practitioners to trace the product back to a specific manufacturer for pharmacovigilance purposes.

In August 2015, FDA released its draft guidance on biosimilar naming. Its proposed framework closely matches the concepts outlined by the WHO. In the draft guidance, FDA proposes adding a four-letter suffix to the end of a biosimilar’s nonproprietary name that is unique and nonpromotional. FDA has requested feedback on whether four-letter suffixes should be random (e.g., devoid of meaning, thereby mirroring the WHO’s proposal) or meaningful (e.g., keyed to the manufacturer’s name) like the placeholder name given to the first FDA-approved biosimilar, filgrastim-sndz. FDA cites avoiding inadvertent biosimilar substitution and facilitating pharmacovigilance as reasons for choosing this naming convention. It has not yet decided whether interchangeable biosimilars will have a suffix or whether they will share the same name as the reference product and has requested stakeholder input on the issue.

\textit{Biosimilar Reimbursement—Centers for Medicare and Medicaid Services}

According to the BPCIA, Medicare will reimburse the cost of a biosimilar product at 100% of the biosimilar’s average sale price (ASP) plus 6% of the reference product’s ASP. This approach was designed to provide a financial incentive (e.g., maintain a profitable margin) to health care practices to use the lower-price product. Recently, the Centers for Medicare and Medicaid Services has clarified its payment policy for biosimilars, stating that it intends to group all biosimilars together (including those designated as interchangeable) separately from the reference product within a single Healthcare Common Procedure Coding System (HCPCS, or J-code) for the reimbursement calculation. Many believe that this policy decision will have negative effects on biosimilar pharmacovigilance, because HCPCS codes within claims data are routinely used to identify specific products for pharmacovigilance (active surveillance) and research purposes (e.g., comparative effectiveness). Grouping biosimilars into a common HCPCS code will facilitate claims administration but will diminish researchers’ capability to correctly attribute a safety signal to a particular manufacturer.

The reimbursement model from Centers for Medicare and Medicaid Services has meaningful implications for the remaining members of the U.S. population, because they often serve as reimbursement models for private payers. However, the way that private payers will approach reimbursement for biosimilars is unknown. One possibility will be driving use toward one specific product, but the concern is that the specific product will not always have the least costly acquisition price because of site-specific contracting. Any reimbursement policy should recognize that different providers will have different acquisition prices for each biological product.

\textit{Issues Related to Pharmacy Practice}

\textit{Operational Challenges}

Because biosimilars are a novel regulatory type of medication product within the United States, pharmacists will face specific operational challenges. These challenges generally fall within the broad categories of formulary analysis, order management and information systems, inventory management, financial analysis, and education. Table 4 summarizes key challenges within each domain.
Table 4. Key Operational Challenges with Biosimilars

<table>
<thead>
<tr>
<th>Domain</th>
<th>Element</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulary analysis</td>
<td>• Product approval pathway and data package</td>
</tr>
<tr>
<td></td>
<td>• Appropriate indications (on label and off label) for use</td>
</tr>
<tr>
<td></td>
<td>• Extrapolation considerations</td>
</tr>
<tr>
<td></td>
<td>• Therapeutic interchange +/- guided use policies</td>
</tr>
<tr>
<td></td>
<td>• Transitions of care</td>
</tr>
<tr>
<td></td>
<td>• Payer mix</td>
</tr>
<tr>
<td>Order management and information systems</td>
<td>• Differentiation of biosimilar and reference product in electronic systems to prevent inadvertent substitution and facilitate pharmacovigilance</td>
</tr>
<tr>
<td></td>
<td>• Ordering of sets, protocols, and MARs</td>
</tr>
<tr>
<td></td>
<td>• Medication reconciliation</td>
</tr>
<tr>
<td>Inventory management</td>
<td>• Buyer’s need for adequate information (NDC code, etc.).</td>
</tr>
<tr>
<td></td>
<td>• Confirmation of whether both biosimilar and reference are in stock</td>
</tr>
<tr>
<td></td>
<td>• Maintenance of product storage and handling conditions</td>
</tr>
<tr>
<td>Financial analysis</td>
<td>• Pricing information comparison (base, contract, reimbursement, margin)</td>
</tr>
<tr>
<td></td>
<td>• Staff management time</td>
</tr>
<tr>
<td></td>
<td>• Patient assistance and out-of-pocket expenses</td>
</tr>
<tr>
<td></td>
<td>• Determination of financial impact</td>
</tr>
<tr>
<td>Education</td>
<td>• Drug information and education to all providers (clinical data, policies, etc.)</td>
</tr>
<tr>
<td></td>
<td>• Patient education materials</td>
</tr>
</tbody>
</table>

MARS = medication administration records; NDC = National Drug Code. Adapted from (Lucio et al., 2013)²⁴

Product Substitution by Pharmacist

For the greatest effect of biosimilars in reducing (or moderating) health care expenditures, a pharmacist should be able to act independently of the prescriber (using professional autonomy and judgment) to substitute the least expensive, pharmaceutically equivalent medication product for the drug prescribed. The success of generic medications in reducing health care costs has been well established, and much of that success can be attributed to the pharmacist’s ability to autonomously substitute these products for the branded drug. The goal is the same for biosimilars, but additional considerations exist for pharmacists when considering whether they should substitute and whether they have received sufficient authority by their respective state to do so.

The first challenge with biosimilar substitution is the standard by which a substitution can be made. For small-molecule drugs, those generally meeting a bioequivalence standard set by FDA are appropriate for substitution. By definition, a biosimilar must be bioequivalent to the reference product, but additional requirements given by FDA include studies of structure and function; human pharmacodynamics studies; and clinical studies demonstrating equivalence to the reference product in safety, efficacy, and immunogenicity endpoints.

As previously mentioned, FDA has defined an interchangeable biosimilar as a product that would be appropriate for a pharmacist to substitute for the reference product because there is no clinical risk in switching between the interchangeable biosimilar and the reference product. FDA has published the Purple Book with a list of all biological products (including biosimilars) and ratings of whether the products are interchangeable with another product.¹ Akin to their use of the Orange Book for small-
molecule drugs, pharmacists are expected to be able to make substitution decisions based on this publication. Switching between a non-interchangeable biosimilar and the reference product is not generally recommended for patients because of concerns regarding immunogenicity. Therefore, if a patient begins treatment with the non-interchangeable biosimilar or the reference product, he or she should continue treatment with the product that was first administered. This approach may present challenges with continuity of care and transitions of care when patients transfer from one setting (e.g., the community) to another (e.g., the hospital or long-term care).

The second challenge with biosimilar substitution is whether state pharmacy practice laws provide a pharmacist with sufficient authority to substitute biological products. Although substitution laws are currently in place for generic drugs, whether the language is sufficiently translatable to biological medications is unclear. Further, some state laws specifically reference the Orange Book as the list of pharmaceutical products deemed appropriate for substitution. Some states have been proactively passing laws to specifically address biosimilar substitution. Although some have argued that these are “biosimilar anti-substitution laws,” the enacted laws generally follow the same framework for generic drugs by mentioning the criteria for product substitution; having a “dispense as written” provision; requiring communication about substitution to the prescriber or patient; and requiring recordkeeping. Because of the concerns noted earlier regarding biosimilar pharmacovigilance, state laws typically require more prescriber and patient communication and recordkeeping.

Table 5 contains examples of these elements from states that have passed biosimilar substitution laws.

Table 5. Examples of State-Level Biosimilar Substitution Laws

<table>
<thead>
<tr>
<th>State</th>
<th>DAW provision</th>
<th>Product’s criteria for substitution and interchangeability</th>
<th>Prescriber and patient communication</th>
<th>Recordkeeping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delaware²⁷</td>
<td>Yes</td>
<td>FDA designated interchangeable product or therapeutic equivalent.</td>
<td>Inform patient; inform prescriber in 10 days.</td>
<td>Same as generic law</td>
</tr>
<tr>
<td>Florida²⁸</td>
<td>Yes</td>
<td>FDA determined interchangeability.</td>
<td>Inform patient same as generic; notify by EMR documentation if practicing in an institution.</td>
<td>2 years</td>
</tr>
<tr>
<td>Virginia²⁹</td>
<td>Yes</td>
<td>FDA determined interchangeability.</td>
<td>Inform patient of cost; inform prescriber within 5 days.</td>
<td>2 years</td>
</tr>
<tr>
<td>Massachusetts³⁰</td>
<td>Yes</td>
<td>FDA determined interchangeability.</td>
<td>Inform patient and prescriber (no timeline).</td>
<td>1 year</td>
</tr>
</tbody>
</table>

DAW = dispense as written; FDA = U.S. Food and Drug Administration; EMR = electronic medical record.

As can be seen from table 5, these state laws provide explicit authority for a pharmacist to substitute an interchangeable biosimilar for the reference product, with stipulations on communication and recordkeeping. Because each state is different in its approach to generic substitution, a similar model could be used for biosimilar substitution on a state-by-state basis, with each state deciding the best approach for communication and recordkeeping. The involvement of practicing pharmacists in crafting the language for such laws is important.
Conclusion

The introduction of biosimilars into the U.S. marketplace is an opportunity to moderate costs related to traditionally expensive medications. Experience in Europe indicates that these products are therapeutically equivalent to their reference products and confer moderate savings. Some policy issues remain unresolved in the United States, such as naming, interchangeability, and reimbursement. Additionally, pharmacists will have responsibility for substituting biosimilars and incorporating them into the medication use process within their practice. Further, survey studies indicate that more education is needed about biosimilars. Thus, pharmacists are also likely to take the lead in educating other health care providers and patients regarding biosimilars within their respective practices.

References

16. U.S. Food and Drug Administration. Guidance for industry: clinical pharmacology data to support a demonstration of biosimilarity to a reference product—draft guidance. Available at:


**Relevant APhA Policies**

**2012, 2007 Biologic Drug Products**

1. APhA encourages the development of safe, effective, and affordable therapeutically equivalent generic/biosimilar versions of biologic drug products, including clinical trials that assess safety.

2. APhA encourages the FDA to develop a scientifically based process to approve therapeutically equivalent generic/biosimilar versions of biologic drug products.

3. APhA should actively support legislation to hasten the development of an efficient regulatory process to approve therapeutically equivalent generic versions of biologic drug products.

4. APhA should initiate educational programs for pharmacists and other health care professionals concerning the determination of therapeutic equivalence of generic/biosimilar versions of biologic drug products.

(JAPhA NS45(5):580 September-October 2007)) (JAPhA NS52(4) 458 July/August 2012)
1991  **Biotechnology**
APhA encourages the development of appropriate educational materials and guidelines to assist pharmacists in addressing the ethical issues associated with the appropriate use of biotechnology-based products.

2005, 1988  **Pharmaceutical Biotechnology Products**
APhA recognizes the urgent need for education and training of pharmacists and student pharmacists relative to the therapeutic and diagnostic use of pharmaceutical biotechnology products. APhA, therefore, supports the continuing development and implementation of such education and training.