Understanding Key Differences Between Biosimilars and Small Molecule Generics

The majority of therapeutic agents used in clinical medicine today are traditional small molecule drugs (SMDs). However, biologics have become prominent in the treatment of many conditions and, over the past 2 decades, the development of biologics has revolutionized the treatment of many diseases, including anemia, diabetes, cancer, hepatitis, multiple sclerosis, rheumatoid arthritis, and inflammatory bowel disease.1-3 More than 100 different biologic therapeutic agents have been approved for use in the United States, with many more in development.4 Because of the differences in size, complexity, and manufacturing methods between SMDs and biologics, there are unique considerations for the development and approval of biosimilars.

Small Molecule Drugs and Biologics

SMDs are inorganic low-weight molecules (typically <1,000 Da) that can be fully characterized by analytical techniques. They produce a desired therapeutic effect via modulation of the structure and function of endogenous biologic materials, usually cell-surface receptors, intracellular signal transduction elements, or circulating proteins.2,5,6 Examples include acetylsalicylic acid and other oral medications. They are relatively stable and are introduced into the bloodstream via varied routes of administration.2 Because of their small size, they are generally distributed widely throughout the body and can permeate cells, thereby exerting their action by modulating intracellular or extracellular elements.2,6

Biologics are proteins derived from living cells and are produced through various processes, such as recombinant DNA, controlled gene expression, or antibody methods (Figure 1).2,7 Examples include specific therapeutic agents such as human recombinant insulin and erythropoietin, as well as classes of agents such as growth hormones and monoclonal antibodies directed against cytokines or cell surface molecules.7,8 Biologics are produced in biotechnological processes via genetic modification of microorganisms, such as yeast or mammalian cell lines.9 Because of their complexity and vulnerability to degradation in the gastrointestinal tract, biologics are administered by injection or infusion.2 Similarly, because of their relatively large size (generally 5 to 200 kDa), most (but not all) biologics have a complex mechanism of action that targets multiple cell-surface sites and encounter more extracellular barriers than traditional SMDs (Figure 2).2,10-19

Because SMDs are synthesized through a series of chemical reactions, the manufacturing process can be reproduced in a fairly reliable manner to yield an identical end product, called a generic.2,9 In this article, generics refer to SMDs where the active ingredient is identical to the small molecule innovator product. Conversely,
biologics are much larger and inherently more complex products produced in living systems (Table 1). Because of this, similar but not exact copies are possible, called biosimilars. The manufacture of biologics from unique cellular-expression systems requires extensive interdisciplinary effort and experience in molecular and cell biology, biochemistry, and protein, biochemical, and industrial engineering. There are many steps in the manufacturing process that can influence the purity, potency, clinical efficacy, and safety of the finished product. Since a protein can be folded in several ways to impart unique physicochemical and immunological characteristics, differences in the source and extraction/purification processes can alter its 3-dimensional structure. These characteristics can be modified by post-translational changes such as glycosylation. Cells are sensitive to their culture environment and so are cultivated via a complex process with strict control of pH, temperature, and oxygen levels. Contaminants and impurities (eg, trace DNA, endotoxins, viral proteins, and unwanted host cell proteins) produced as a result of the manufacturing process are removed via several purification steps.

Generic Drugs and Biosimilars

Governments and regulatory agencies throughout the world have processes by which new SMDs can be manufactured and sold exclusively by the developer for a certain period of time. This system creates a favorable economic environment for the development of new SMDs by providing an avenue for the manufacturer to recoup research and development (R&D) costs. However, after expiration of the patent period, other companies can develop and market generic formulations of the original SMD. Because development of generic compounds is associated with lower up-front R&D costs than development of innovator SMDs, they typically are less expensive, resulting in an economic incentive to payers and consumers to switch to the generic form of the drug.

Because generics are SMDs where the active ingredient is chemically identical to the product they copy, the regulatory requirements for approval of a generic are more abbreviated when compared to the original innovator SMD. In the United States, an Abbreviated New Drug Application (ANDA) process, as outlined by the US Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Act of 1984), states that large clinical trials for safety and efficacy are not required. Thus, companies that develop generic products can rely on the FDA’s previous findings of safety and effectiveness for the innovator drug, and the generic drug approval is based on the principles of “sameness” (ie, the same active ingredient, identical in dose, strength, route of administration, safety, efficacy, and intended use). Large-scale clinical trials are not required and generic drugs only need to show bioequivalence to the innovator drugs typically based on pharmacokinetic parameters, such as the rate of absorption or bioavailability in at least 24 to 36 healthy volunteers.

Similar to the patent system for SMDs, developers can obtain exclusive rights to the manufacture and distribution of their innovator biologic agent for a period of time, thereby increasing

![Figure 1. Recombinant protein production: sources of variation between manufacturers.](From reference 7.)
the likelihood of recouping up-front R&D costs.\textsuperscript{8,23-25} After expiration of the patent period, competitors have the option to develop and market “biosimilar” drugs. The FDA defines a biosimilar drug as “a biological product that is highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences from the approved biological product in terms of safety, purity, and potency.”\textsuperscript{26} While manufacturing steps may be similar between different manufacturers of biologics, they will not be identical. Moreover, because of differences in unique cell lines, glycosylation patterns, and the inherent sensitivity of the cells to differences in nutrients and environment, the same biologic manufactured by 2 different companies may be different in a number of ways.\textsuperscript{27} For this reason, regulatory authorities around the world have developed separate approval pathways for biosimilars. The rest of this review will discuss the global regulatory outlook for biologics and biosimilars and the development of an abbreviated regulatory pathway for biologics in the United States.

**Global Regulatory Pathways For Biosimilars**

**European Union**

The European Union has led the way in establishing regulations for biosimilars (sometimes called “follow-on biologics” in Europe), including a directive outlining the process to gain regulatory approval for these agents. In 2005, the European Union and the European Medicines Agency (EMA) established the first regulatory pathway for biosimilars that is distinct from the generic pathway.\textsuperscript{28} There are 3 scientific guidelines issued by the EMA that have established a process for demonstrating similarity between a biosimilar product and the reference innovator product.\textsuperscript{28} First, the EMA issued an overarching guideline in 2005 that defined biosimilars and established a process for demonstrating similarity between a biosimilar product and the reference innovator product.\textsuperscript{29} The second guideline addressed quality issues (physicochemical properties, biological activity, and purity), and the third described nonclinical and clinical issues.\textsuperscript{30,31} A separate set of distinct guidelines established detailed data requirements for class-specific products, including recombinant follicle-stimulating hormone, recombinant interferon-beta, monoclonal antibodies, recombinant erythropoietins, low-molecular-weight heparins, recombinant interferon-alpha, recombinant granulocyte colony-stimulating factor, somatotropin, and recombinant human insulin.\textsuperscript{28} These class-specific guidelines outlined the nonclinical and clinical requirements, and recommended study designs and postmarketing commitments. All of these guidelines, including updates, revisions, and appendices, are currently available through the EMA website (http://www.ema.europa.eu). The first biosimilars were approved and marketed in Europe in 2006, and there are currently 6 on the market, including 1 epoetin alfa, 3 filgrastims, 1 epoetin zeta, and 1 somatropin.\textsuperscript{32,33}
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and giving the FDA the authority to approve biosimilars under
similar to or interchangeable with an FDA-approved biologic drug,
approval pathway for biological products that are highly simi-
lar.36 At the end of March 2010, the United States enacted the Biologics Price Competition and Innovation (BPCI)
Act. However, submission of the BLA could only be achieved
after sufficient clinical trials had been performed to obtain mar-
keting approval.35 (Full WHO guidelines are available at http://www.who.int/biologicals.)

This guideline describes a stepwise approach, starting with
characterization of quality attributes of the product, followed by
nonclinical and clinical evaluations. The WHO guidelines indi-
cate that manufacturers should submit a full quality dossier that
includes a complete characterization of the product, the demon-
stration of consistent and robust manufacture of their product,
and the comparability evaluation between the biosimilar and the
reference biologic agent in the quality part, which together serve
as the basis for the possible reduction in data requirements in the
nonclinical and clinical development phases.35 (Full WHO
guidelines are available at http://www.who.int/biologicals.)

**United States**

Prior to 2010, the only approval pathway for a biosimilar
was to file a full Biologic License Application (BLA) as a new
biologic agent under 351(a) of the Public Health Service (PHS)
Act. However, submission of the BLA could only be achieved
after sufficient clinical trials had been performed to obtain mar-
keting approval.36 At the end of March 2010, the United States
enacted the Biologics Price Competition and Innovation (BPCI)
Act (Table 2), amending the PHS Act to establish an alternate
approval pathway for biological products that are highly simi-
lar to or interchangeable with an FDA-approved biologic drug,
and giving the FDA the authority to approve biosimilars under
the new section 351(k) of the PHS Act.34,37,38 Through this new
approval pathway, biological products are approved based on
demonstrating they are biosimilar to a biological product that
is already approved by the FDA, which is called a reference
product.26

The designation of interchangeability is one critical area in
which the US law differs from that of the EU and all other juris-
dictions. The law defines interchangeable to mean that the
biosimilar product may be substituted for the reference prod-
uct without the intervention of the health care provider who
prescribed the reference product.37,38 Once approved, most
generic drugs can be substituted automatically for the refer-
ence product without the intervention of the healthcare pro-
vider in many states. However, for biosimilars, a product must
be designated as interchangeable before such a substitution
can occur automatically without any notification. To achieve
the interchangeability designation, a product is first determined
to be a biosimilar, and then may be considered for a determi-
nation of interchangeability with the reference product. Deter-
mination of interchangeability not only requires demonstration
of biosimilarity, but also that the product is expected to pro-
duce the same clinical result in any given patient and presents
no additional risk to safety or efficacy as a result of switching
between the biosimilar and the reference product.37,39

On Feb. 9, 2012, the FDA announced the publication of
draft guidance documents to assist the industry in develop-
ing biosimilar products.26 The abbreviated Biologic License
Application pathway guidance consists of 3 documents, one
each covering the scientific and quality considerations in dem-
onstrating biosimilarity and the other a question and answer
section discussing implementation of the BPCI Act (“Scientific
Considerations in Demonstrating Biosimilarity to a Reference
Product,” “Quality Considerations in Demonstrating Biosimi-
larity to a Reference Protein Product,” and “Biosimilars: Ques-
tions and Answers Regarding Implementation of the Biologics
Price Competition and Innovation Act of 2009,” respectively).40

Similar to the requirement of the EMA, a number of factors
are considered important by the FDA when assessing

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**Table 1. Comparison of Traditional Small Molecule Drugs and Biologic Agents**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Small Molecule Drug</th>
<th>Biologic Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Example</strong></td>
<td>Acetylsalicylic acid (180 Da)</td>
<td>Monoclonal antibody (~150,000 Da)</td>
</tr>
<tr>
<td><strong>Entity</strong></td>
<td>Chemical</td>
<td>Protein</td>
</tr>
<tr>
<td><strong>Structure</strong></td>
<td>Small, simple, well characterized</td>
<td>Large, complex, heterogeneous</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>Stable</td>
<td>Unstable</td>
</tr>
<tr>
<td><strong>Mode of administration</strong></td>
<td>Usually amenable to ingestion</td>
<td>Usually requires injection or infusion</td>
</tr>
<tr>
<td><strong>Manufacturing process</strong></td>
<td>Predictable and precise method; identical copies in batches</td>
<td>Living cell-based complex technology; batch-to-batch variation, sensitive to storage and handling</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Mostly nonimmunogenic</td>
<td>Immunogenic</td>
</tr>
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Adapted from references 2 and 9.
41 Therefore, by integrating various types of information, including structure, function, animal toxicity, human PK and PD, human immunogenicity, and clinical safety and effectiveness, the FDA indicated that the agency wished to consider the “totality of the evidence” provided by the manufacturer. This suggests that, due to the complexity of biologics, the FDA will rely heavily on scientific justification and rationale when making decisions on what types of additional studies are needed for biosimilar approval.

In the draft guidance it is noted that a clinical program for a 351(k) application must include a human trial or trials sufficient to demonstrate safety, purity, and potency in one or more appropriate indications for which the reference product is licensed. At least 2 trials generally will be required for a biosimilar, one examining the PK and PD and the other evaluating the safety and efficacy as well as addressing any immunogenicity issues.

### Considerations and Exceptions

There are several considerations related to this abbreviated approval pathway. First, some older biologics, such as human recombinant insulin and growth hormone, were approved as new drugs through the New Drug Application 505(b)2 pathway, under the Federal Food, Drug, and Cosmetic Act. That act allows the FDA to rely on published scientific literature or its previous findings for similar products as the basis for approval. Thus, biosimilars of those older biologics might not necessarily follow the newer abbreviated approval pathway, but instead could be approved under an abbreviated pathway similar to that for generics. The FDA's position on this is unclear.

The second consideration is that some manufacturers have chosen to proceed with applications for regulatory approval through the BLA pathway designed for innovator biologic agents. As an example, the biologic agent, Tbo-filgrastim (XM02 filgrastim) for the management of neutropenia, was submitted and approved under the standard BLA in the United States in August 2012.

The third consideration is that the draft guidance documents indicate that the FDA has not settled some important biosimilars policy questions, including exact requirements for demonstrating interchangeability of a biosimilar with a reference product. Thus, while the FDA continues to consider

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**Table 2. Requirements of the Biologics Price Competition and Innovation Act of 2009**

<table>
<thead>
<tr>
<th>Issue</th>
<th>Requirements</th>
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| Establishing biosimilarity | 1. The biologic product is highly similar to the reference product, notwithstanding minor differences in clinically inactive components. This determination is based on data from analytical studies, animal studies, and a clinical study or studies.  
2. No clinically meaningful differences exist between the biological product and the reference product in terms of the safety, purity, and potency of the product. |
| Interchangeability      | 1. The biosimilar can be expected to produce the same clinical result as the reference product in any given patient.  
2. For products that are administered more than once to the patient, switching between innovator and biosimilar products is safe and efficacious. |
| Mechanism of action     | The biosimilar and the reference product have the same mechanism of action for the condition(s) prescribed, recommended, or suggested in the labeling. |
| Indications             | The condition or conditions of use prescribed, recommended, or suggested in the labeling. |
| Route/dose/strength     | The route of administration, dosage form, and strength of the biosimilar product are the same as those of the reference product. |
| Exclusivity             | 12 years of data exclusivity for innovator products. |

Adapted from references 37 and 38.
what type of information ultimately will be required to demon-
strate interchangeability, manufacturers seeking an inter-
changeable designation for their biosimilar product likely will
be required to provide a higher level of data than for a biosim-
ilar approval without an interchangeable designation.55,46 Currently, state laws provide guidance for pharmacists regarding substitution of generics with or without consulting the provider. Once the FDA has established detailed guidelines for interchangeability, there may be similar regulation for biologics at the state level.47

**Pharmacovigilance**

As biosimilars become available, it will be important to deter-
mine how adverse events (AEs) will be tracked and accurately
attributed to the correct product and manufacturer.27 Ideally, a
method to accurately record the specific drug, manufacturer,
and drug lot would be optimal. This will require an evolution in
health technology platforms to capture and seamlessly provide
this information to treating health care professionals, manufac-
turers, and regulatory bodies. Until that time, collection of accu-
rate post-approval data will rely on product identifiers to
distinguish between biologic products.41

According to the EMA, elements of a proposed biosimilar pharmacovigilance system include qualified staff, identification of the organization and locations of activities and databases, documented data collection procedures, and mandatory reporting of individual case safety and general safety updates.48 In 2002, the EMA introduced the European Risk Management Strategy, a program aimed at strengthening safety monitoring of medical products by promoting early detection, assessment, minimization, and communication of risks. Even though the EMA guideline addresses a host of issues surrounding biosimilars, national and local involvement still will be necessary.49 The current EU and US pharmacovigilance systems rely heavily on vol-
untary and spontaneous reporting. However, only a minority of
AEs are ever reported and the quality of these reports may vary and do not always identify the product in question.50,51

Improvements in these systems will depend on the ability of the reporter (either health care provider or patient) to correctly iden-
tify and report the associated product. A robust post-approval safety surveillance program will have to include precise AE track-
ing and tracing capabilities to detect and evaluate potential issues and promote efficient and coordinated responses. This will be predicated on the requirement of specific nomenclature of each biosimilar, including a unique nonproprietary name, Healthcare Common Procedure Coding System (HCPCS)/National Drug Code (NDC), and lot number.7,51-53

The FDA has not released a guideline on how biosimilars will be named. Generics do not go through the U.S. Adopted Names Council process and are automatically assigned the same non-
proprietary name as the innovator product. The challenge of bio-
similars is that each innovator biologic agent may have multiple biosimilars, and each of those biosimilars can have its own variant characteristics.54 Thus, a distinguishable United States Adopted Name may aid in keeping product post-approval data distinct.

Protocol-based switching between SMDs and their formu-
larly generic or nongeneric equivalents is an important and
widespread strategy within health care systems as a method
of containing costs. Due to potential differences, switching between innovator biologics and biosimilars will require a much
more comprehensive formulary decision-making process than
generic substitution, taking into account whether the FDA has
determined a product to be interchangeable.7 This decision
process may involve reviewing available data and indications as well as considerations including manufacturer services. The ability of a manufacturer to provide consistent supply is an important consideration.55

Potential switching also poses challenges for tracking which product a patient has received, making attribution of AEs difficult.53 This is especially important if the immunogenicity profile of the product changes over time. The current surveil-
lance methods available are limited in that they only allow for
qualitative event signals and do not indicate the frequency of
an AE in a given population.52 Systematic and ongoing safety monitoring systems will be necessary to recognize and eval-
uate the effect of intrinsic differences in immunogenicity and
the detection of rare AEs unique to a particular product.51,52,56

These systems would be practical and encourage reporting by
healthcare professionals, provide manufacturers with a frame-
work to monitor and report events, and ensure traceability of
AEs to the specific product in question.53

**Pharmacy Education on Biosimilars**

The clinical use of biosimilars is a new and complex field, and
the standards of care regarding their use have not been defin-
itively established. Pharmacists will play a vital role in directing
the use of biosimilars and in disseminating information to the
other members of the clinical team.

Yet, there is a significant knowledge gap for health care profes-

cionals with regard to regulatory pathways; a survey of 277
physicians, nurses and pharmacists, and other clinicians con-
ducted by the National Comprehensive Cancer Network (NCCN)
Work Group revealed that more than half were either not at all
familiar or only slightly familiar with recent developments sur-
rounding biosimilars, a fact that points to the necessity of edu-
cation about these medications.27 Marcie Bough, senior director of
government affairs, American Pharmacists Association, who
spoke to the FDA during a public hearing in 2012, echoed this
sentiment, commenting, “Pharmacists need additional guidance
on the handling of biosimilar products in the pharmacy when
these products become more widely available following the
approval of the biosimilar pathway.”57 It is incumbent on phar-
macists to familiarize themselves with the regulatory and clinical
aspects regarding biosimilars.

The American Society of Health-System Pharmacists (ASHP)
is highly engaged in advising the FDA in establishing the biosim-
ilar regulatory process, with the goal of assuring that patients
have access to safe, effective, and less expensive biologic ther-
apies. ASHP has launched an educational initiative (http://www.
biosimcentral.org) to provide an in-depth review of the various
clinical and regulatory aspects concerning the introduction of
biosimilars in the United States. A primer on biosimilars also is
available online (http://www.ashpmedia.org/symposia/biosim-
series/primer), and ongoing continuing education opportunities are
available at ASHP meetings.

**Conclusion**

Biologic therapeutics have revolutionized the treatment of
many diseases, and biosimilars will have similar therapeutic effi-
cacy with potentially lower costs to the health care system. The
complexity of the manufacture of biologics makes the development of biosimilars more complex than the development of generics. Because of this complexity, the regulatory pathway required for biosimilar approval is distinct. The EMA and the WHO paved the way in establishing regulatory guidelines for biosimilars. The FDA draft guidelines emphasize a “totality of evidence” approach by which various types of information, including structural and functional characterization, nonclinical evaluation, human PK and PD data, clinical immunogenicity data, and clinical safety and effectiveness data will be considered as part of a biosimilar application. Biosimilars will likely require a more extensive formulative evaluation than generics when used for protocol-based switching, and pharmacists will play a key role in considering the available data, indications, and other considerations. Pharmacists will also play an important role in establishing systematic and ongoing safety monitoring systems to detect AEs and attribute them to the respective product as biosimilars enter the larger patient population.

References


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