

The Complexities of Biosimilars and the Regulatory Approval Process

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Previously untreatable diseases can now be managed effectively in this medical era of tremendous innovation in pharmaceuticals, thus improving the quality of care and outcomes for patients. At the top of this list of novel and valuable therapies are the numerous biologic drugs used in oncology care, such as the hematopoietics; agents such as filgrastim and pegfilgrastim; and the monoclonal antibodies rituximab, bevacizumab, and trastuzumab. These therapies are extremely valuable in terms of the patient benefit they provide. Their value can also be characterized in the billions of dollars associated with their prescribing and use. Biologics dominate the top-selling drugs by sales in the United States and in other markets globally. In 2017, 11 of the top 15 best-selling pharmaceuticals (73%) were biologics.¹

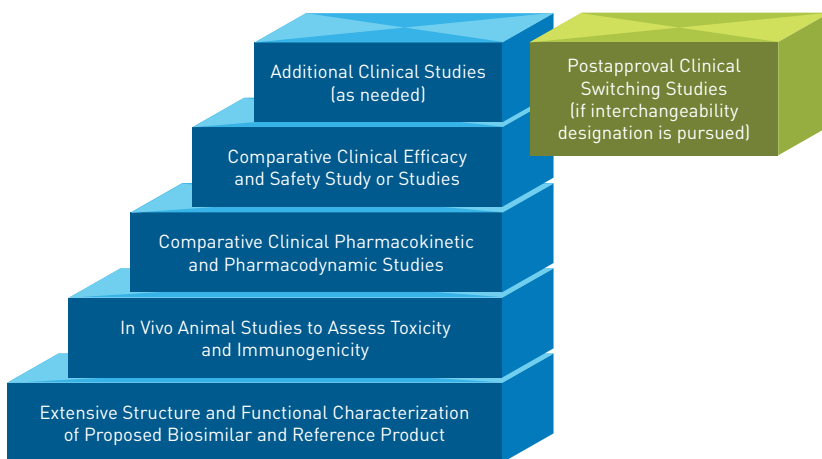
The correlation of commonly used medications and the expense of their use is not a novel concept, but an issue that has been managed for many decades via the generic drug approval process. After a period of patent protection and marketing exclusivity, competing suppliers receive approval for generic versions of previously licensed originator medications to preserve and expand the use of molecules, reduce the cost allocated to these treatments, and free overall healthcare dollars for the next iteration of new therapies. Unfortunately, the generic methodology for small-molecule drugs does not apply to the existing environment of biologics. Compared with small-molecule drugs, biologic drugs are much larger molecular weight molecules with complex biochemical structures (eg, peptides, proteins, antibodies, vaccines).²⁻⁴ Biological products are manufactured in living systems (eg, bacterial or yeast cell lines) or extracted from biological matrices (eg, blood and blood components). Perhaps most importantly, all biologic medications, unlike generic drugs, vary over their lifecycles, which makes the concept of an “identical” product inappropriate for this market. To understand how these inherent properties are managed to ensure the approval of highly similar products, even across oncology disease states, the concepts, processes, and regulatory requirements that exist to support the desired outcome of less expensive biologics of comparable safety and efficacy will be discussed.

ABSTRACT

Created via the Biologics Price Competition and Innovation Act, the biosimilar class of drugs was conceived as an opportunity to introduce competition for commonly used biologics following loss of patent protection and market exclusivity, similar to the generic paradigm that has helped sustain access and innovation for more than 3 decades. The FDA approves a biosimilar after a manufacturer establishes that the product is highly similar to a previously approved originator biologic reference product without any clinically meaningful differences in safety, purity, and potency. Given the concerns about increasing healthcare costs and this new opportunity to reduce the expense associated with biologics, including many commonly used oncology medications, the use of biosimilars will likely increase as numerous stakeholders, including managed care organizations, begin to implement policies to encourage adoption. As biosimilars are a relatively new class of drugs, clinical, scientific, and regulatory aspects continue to evolve and improve. Understanding those various aspects can improve clinician acceptance and advance the science of biologics and biosimilars. In this report, various factors are addressed to improve the knowledge of biosimilars, including clinical, manufacturing, and cost considerations.

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FIGURE. Stepwise Approach to Biosimilar Development⁷

Definitions/Descriptions and Regulatory Aspects

The potential for a biosimilar class of drugs came into existence via the Biologics Price Competition and Innovation Act (BPCIA) of 2009, itself a part of the Patient Protection and Affordable Care Act.^{5,6} The designation of biosimilars is defined in relation to a reference product in an FDA licensure application such that the biosimilar is “highly similar to the reference product” and that a biosimilar does not differ in a “clinically meaningful” way from the reference product with respect to “safety, purity, and potency.”^{5,7} The BPCIA created an abbreviated, yet extremely rigorous, regulatory approval pathway for biosimilars as a mechanism to promote innovation and competition in the development of biologics and to open an avenue to lower their cost.⁸ In practice, 2 phrases in the FDA’s working definition of a biosimilar are emphasized: “highly similar” and “no clinically meaningful differences.”⁷ These phrases highlight the fact that, unlike small-molecule generics, biosimilars are not identical to their reference products. Given the simplicity of their molecular structure and the well-defined processes for chemical synthesis, the active ingredient in a generic drug product is chemically identical to the brand name product.⁹ Given the consistency and simplicity of the molecular structure, the FDA usually classifies generic drugs as therapeutically equivalent when bioequivalence to the brand name product is established.⁹ This equivalence reinforces the concept that a generic drug is intended and expected to behave in the exact same way as its branded counterpart. On the other hand, this level of exactness does not exist for biologics, originator or biosimilar, given the size, complexity, and processes by which these pharmaceuticals are manufactured.^{3,10} As specified above, biologics are complex, high-molecular-weight molecules that are produced through a living organism, which introduces variations throughout the lifecycle of the biologic. Some variations in the molecular structure of a biologic

are less consequential. However, other changes, such as in the primary amino acid sequence of the biologic or in the biologic compound, including posttranslational modifications, such as glycosylation and deamidation, could greatly alter the stability, functioning, and safety profile of these agents.^{11,12} Biologic manufacturing is closely monitored such that these changes do not result in negative patient outcomes over the lifecycle of the originator. Biosimilars, which are manufactured using different cell lines under different development conditions, will also vary. As a result, the focus of the biosimilar approval pathway is to provide similar assurance that these differences do not impact the clinical performance of the resulting product in relation to the originator brand biologic.^{11,12}

When a biopharmaceutical company obtains approval for a new biological product, their product is recognized as the originator reference to which subsequent agents will be compared. Similar to small-molecule drugs, the manufacturer enjoys a period of market exclusivity for that biological product, and the length of that exclusivity period may vary depending on a host of factors, some of which will be described in subsequent sections of this activity. Given the enactment of the BPCIA and the construction of the related approval pathway, another manufacturer can now pursue development of a biosimilar once that period of exclusivity ends. The BPCIA and guidance documents from the FDA describe the streamlined approval approach for biosimilars.^{5,7} The FDA guidance on demonstrating biosimilarity recommends a stepwise approach for potential biosimilar products (Figure).⁷ To gain approval as a biosimilar, the manufacturer must demonstrate that their product does not differ in a “clinically meaningful” manner from the reference product. The biosimilar approval pathway, also known as a 351(k) application, is more targeted in that it requires fewer clinical studies compared with the reference biological product, which is intended to hopefully translate to lower costs—for the manufacturer, the provider, and most importantly, the patient.⁸ It must be noted, that while the clinical data requirement is reduced, the approval process is no less comprehensive or rigorous. Instead, the testing of a biosimilar includes a greater emphasis on analytical studies to demonstrate similarity with the biological reference product.⁸ Data from animal studies are still required to assess toxicity and from clinical studies to gauge efficacy, immunogenicity, and pharmacokinetics/pharmacodynamics.^{7,8}

One of the critical foundational elements of the biosimilar approval process is known as a “stepwise approach.” This concept conveys that each successive step of approval is focused on any unanswered regulatory questions from prior steps. This methodology supports that efficiency of approval in every succeeding

step addresses “residual uncertainties” from previous sequences in the evaluation, thus supporting more targeted investigations as the process continues.

The other companion concept that supports the foundation of the biosimilar experience is that of the “totality of the evidence.” Each step of the approval mechanism is not evaluated in isolation, but instead is viewed in aggregate to form a total perspective of the biosimilar molecule, providing additional efficiencies that are scientifically sound and ideally lead to lower development cost.

The generic paradigm is greatly facilitated by the fact that competing versions of a small molecule medication share the same non-proprietary (ie, generic name) of the originator, thus making correlation between products much easier. This standard is different for biosimilars. Given concerns about the ease of pharmacovigilance and the potential for inadvertent substitution of highly similar, yet non-identical biologics, the FDA has finalized a strategy in which biosimilars, and ultimately all originator biologics, will have a modified non-proprietary name. For example, the branded biologic Remicade is also identified by its non-proprietary name of infliximab. Rather than being known simply by that designation, the approved biosimilars of Remicade are known respectively as infliximab-dyyb, infliximab-abda, and infliximab-qbtx. In this model “infliximab” represents the core name shared by the originator and the biosimilars which combined with a four letter, “devoid of meaning” suffix, creates a unique “proper” name for each biologic. Prior to finalization of this approach, the FDA approved one biosimilar, filgrastim-sndz, with a suffix that did convey a meaning, the product’s manufacturer. The FDA has since continued to apply the devoid of meaning approach for biosimilars and even for newly approved, novel biologics. The presence of this modifier is relevant for accurate reflection and presentation of medication information in electronic medical records and computerized prescriber order entry systems.

A beneficial aspect for oncology practitioners is that the biosimilar paradigm is no longer just theoretical, but has actually resulted in the licensing of products via the pathway described above. The first biosimilars for oncology for the specific treatment of cancer, one for bevacizumab and one for trastuzumab, were approved in 2017, although neither is presently marketed due to originator patent protections and market exclusivities.^{13,14} However, filgrastim-sndz, a supportive care product, was the first biosimilar approved by the FDA and is increasingly used in place of the reference product, filgrastim.^{15,16} This specific experience has hopefully served to enlist additional trust in the biosimilar mechanism and prepare oncology physicians and other prescribers for an increasing pipeline of competing products. Still, recent information highlights

TABLE 1. Posttranslational Modifications and Common Consequences (examples)²⁶

Posttranslational Modification	Common Consequences
Glycosylation	Multiple effects, such as protein folding, protein targeting/trafficking, ligand recognition/binding, biological activity of the protein, affecting half-life
Disulfide linkages	Stabilize and maintain tertiary and quaternary structures of proteins and multi-subunit proteins
γ-carboxylation and β-hydroxylation	Facilitate calcium binding, particularly in blood factor proteins
Amidation and sulfation	May contribute to peptide–protein stability, activity, or protein–protein interactions

the numerous practice areas that must continue to be addressed to facilitate the introduction and adoption of biosimilars and minimize any misunderstandings that could unnecessarily curtail use.^{17,18} In addition to the products that have reached the market, healthcare professionals (HCPs) should expect the approval of additional versions of those same molecules as well as oncology biosimilars for products including rituximab, cetuximab, and pegfilgrastim.¹⁹⁻²³

Manufacturing and Assessment Methods

The ability to use recombinant DNA techniques to direct cells to manufacture proteins of interest, coupled with industrial-scale cell culture techniques, has led to the success in producing biological products including biosimilars. Although a range of prokaryotic and eukaryotic cell lines have been used for producing biological products for therapeutic use, one of the most common cell lines is the Chinese hamster ovary cell.^{24,25} Mammalian cell lines tend to produce acceptable posttranslational modifications for human use.²⁵ Some examples of common posttranslational modifications include glycosylation, carboxylation, hydroxylation, amidation, sulfation, and disulfide bond formation (Table 1²⁶), all of which can affect the performance of a biological product, including immunogenicity.²⁵⁻²⁷

Characterization

As introduced above, there are many efficiencies that support the biosimilar approval process and enable a more targeted and ideally less expensive development of comparable biologics. First and foremost is the use of analytical characterization tools to examine the structure and function of the biosimilar to validate its safety, purity, and potency. Although physicians and other HCPs are trained to rely on and demand clinical trial data in every circumstance, the expansion and innovation in analytical characterization techniques greatly limits the extent to which this is necessary. Numerous technologies allow for the rigorous assessment of a biologic, including the primary amino acid structure and sequence; secondary, tertiary, and/or quaternary structure; polarity and/or charge; glycosylation and other posttranslational

modifications; and molecular weight.^{28,29} Although clinical trials are subject to numerous factors that could affect the resulting outcome of a study, analytical characterization provides a specific, sensitive, and reproducible methodology to assess a biologic at the level of its structural subunits. These capabilities apply to the chemical structure of a biologic and the way in which it actually works (ie, its function). Functional characterization includes target/receptor binding and bioactivity via a variety of specialized assays, which demonstrate that a biosimilar is working in the same manner as an originator reference comparator.^{28,29} The use of these types of technologies and their ability to support licensing of safe and effective products has been demonstrated with the approval of the biosimilar filgrastim. It has also been demonstrated in the continued safety and efficacy of originator brands.

As stated above, all biologics vary, including originators. Over an originator biologic's lifecycle, variation is introduced to the molecule as a result of using living organisms to manufacture the biologic. In addition, the manufacturer may make other changes to improve yield, increase purity, or relocate production. These modifications introduce variability. However, the consistency of the product before and after each change is monitored using analytical techniques, such as those that are being employed for biosimilars. As a result, there can be higher confidence in the use of these technologies and their ability to limit the amount of redundant clinical trial information required to support approval. In addition to analytical characterization techniques, another critical element of biosimilar approval efficiency is the concept of indication extrapolation.

Extrapolation

As mentioned above, all clinicians are conditioned to seek and demand clinical trial data when dealing with the approval of medications. This expectation must be treated differently when describing biosimilars. As was just stated, the incredible capabilities of analytical characterization techniques help us ensure, with high sensitivity and specificity, that a biosimilar is highly similar to its originator reference branded counterpart. However, for biosimilars, clinical trial data are still required, but in a more targeted sense. In other words, clinical trial data for a biosimilar of the size and scope of the originator should not be expected, and this is a key area to highlight for clinicians who may be used to seeing more data with originator branded products. It is important to educate HCPs about why there are fewer data available for biosimilars, so that they can become more comfortable with it. If such an expectation existed, the cost of developing a biosimilar would approach that of the originator, which would invalidate the concept of introducing less expensive competition. As a result, when navigating the streamlined 351(k) biosimilar approval pathways, biosimilar manufacturers use the concept of extrapolation to gain approval for their products. Extrapolation is the process of

using clinical trial information in a sensitive and relevant indication to support the opportunity for licensing across the other uses that are not directly studied in a separate clinical trial.^{7,30,31} Manufacturers work with regulators, such as the FDA, to develop clinical trials of adequate size, relevance, and sensitivity to enable extrapolation. The totality of evidence of analytical characterization, animal studies, pharmacokinetics/pharmacodynamics trials, immunogenicity testing, and clinical data in a sensitive indication can all support the extrapolation of indications to uses not directly studied in clinical trials.³¹ Extrapolation has been adopted successfully throughout the decade-plus history of the biosimilar market in the European Union. It has also been used in every biosimilar approval that has taken place in the United States.^{30,32} Data, especially from the European market, highlight that the use of a biosimilar in an extrapolated indication provides the same clinical outcomes as the originator.³³ Although we can learn about biosimilars from the European experience with these products, the concept of agents that are not just highly similar, but also formally designated as interchangeable is a uniquely American issue that we will discuss in the next section.

Interchangeability

Besides establishing the biosimilar class of drugs, the BPCIA introduced the designation of interchangeability, which has been the subject of tremendous concern and conversation as the biosimilars concept has continued to mature.⁵ The understanding of what interchangeability means is critical. There is an important distinction between biosimilars and interchangeable biologics. An interchangeable biologic (ie, a biosimilar that has received this additional designation) is not inherently superior to a noninterchangeable biosimilar. It simply means that the interchangeable biologic has shown through additional information that switching a patient back and forth between it and the originator produces the same outcome as if a patient were left exclusively on the brand. Second, because of this understanding, the FDA states that a pharmacist could substitute the interchangeable biologic for the originator without the intervention of the prescriber.

This last element has driven substantial concern for prescribers and could make some HCPs apprehensive about these agents. There are 2 important elements to consider. First, the FDA is not the ultimate arbiter of how drug substitution occurs. State pharmacy practice acts and regulations govern under what circumstances substitution occurs and many states have enacted requirements for physician notification, patient consent, and recordkeeping to address and manage these conditions when interchangeable biologics are ultimately approved. Second, most of the commonly used biologics for which biosimilars are being developed are products infused in a hospital outpatient or physician office setting or delivered through specialty pharmacy. As a result, the use of these drugs is managed through protocols and

formulary requirements and usually necessitate some level of prior authorization requiring additional prescriber intervention.

In January 2017, the FDA released a draft guidance for the industry regarding what data and information would support the designation of interchangeability.³⁴ Although it is not a final guidance, the FDA suggests a stepwise approach for approval building from basic in vitro studies up through clinical immunogenicity studies, followed by additional clinical studies as needed.³⁵ The FDA’s guidance emphasizes that other data and information will be considered in accordance with the FDA’s “totality of the evidence” approach to reviewing applications.³⁴ The guidance, however, seems to caution applicants about deviating too far from the style of device used for the reference biological product out of concern for the impact on the ability of end users to adapt.^{8,34} One of the most concerning issues in the FDA’s guidance document is the request for a specific switching study. Prior to publication of the draft guidance document on this issue, there was some thought that pharmacovigilance data collected post-approval of the non-interchangeable biosimilar could be used to support a subsequent filing for interchangeability. However, FDA has stated that a specific “switching” study would be required, which has created some concerns about additional development expense. As part of the process of soliciting comments from the public, a range of concerns has been expressed about the interchangeability guidance from various entities, including biopharmaceutical manufacturers, trade groups, pharmacy groups, and physician groups, among others.³⁶⁻³⁹ The major concerns focused on the following issues: switching studies; extrapolation for additional indications; labeling and naming; efficacy endpoints; and postmarketing studies.³⁶⁻³⁹ Of note, the FDA draft guidance on interchangeability is not yet finalized, pending public comment.

Lessons from Europe

One of the goals for establishing a biosimilars class of drugs is to promote price competition. As biosimilars enter the US market, the effect on the cost of therapy will be scrutinized and evaluated. The European Medicines Agency (EMA) establishes a framework for the approval of drugs (including biosimilars) and individual countries within the European Union create laws and regulations governing how those drugs are dispensed. The EMA approved the first biosimilar in 2006, nine years before the FDA, and the EMA has approved more biosimilars continent-wide.⁴⁰ Europe’s experience with biosimilars may provide insights regarding regulation, safety, market penetration, and cost savings. Similar to the American Society of Clinical Oncology statement on biosimilars,¹⁷ the European Society for Medical Oncology published a position paper on the

TABLE 2. Examples of Updated Biologic Products⁵⁰

Originator Biologic	Updated Biologic Product	Quality Improvement
Filgrastim	Pegfilgrastim	Pegylation allows for less frequent dosing
Trastuzumab	Trastuzumab emtansine	Antibody–drug conjugate for improved efficacy compared with antibody and drug separately
Antihemophilic factor (recombinant)	B-domain deleted recombinant factor VIII, Fc fusion protein	Increased half-life allows for less frequent dosing

Selected products adapted from reference 50.

use of biosimilars in oncology in which similar concerns are raised about labeling, extrapolation, interchangeability, and other issues.⁴¹

As stated above, the EMA does not have a separate formal designation of interchangeability.⁴² Each EU member state, however, sets regulations for substitution of drugs and, thus, the issue of biosimilar substitution and interchangeability will be governed at that level.^{41,42} In the United States, regulations for the dispensing of pharmaceuticals reside at the state level. Several US states have passed laws to regulate how interchangeable biologics are dispensed, even though an interchangeable biologic has not yet been approved by the FDA.⁴³ On the other hand, regulatory agencies of several EU countries (eg, the Netherlands, Finland, Germany, Ireland, and Scotland) have endorsed the concept of interchangeability with prescriber supervision.⁴⁴ Such comparisons are helpful when analyzing the economics of biosimilars in Europe for comparison and projections to the United States.

Continued Market Development

In addition to the official classifications of biological products, biosimilars, and interchangeables, the term biobetters has been circulating in recent years. A biobetter is not an official FDA drug class. Rather, biobetter is essentially a marketing term that generally refers to a biological reference product that has been modified to improve the drug in some measurable manner, such as improved pharmacokinetics, better safety, and/or better efficacy, among others.^{45,46} The resulting biobetter is a new biological drug product that requires the same regulatory approval process as a reference biological product.⁴⁵⁻⁴⁸ Common mechanisms to achieve better properties include conjugating polyethylene glycol or albumin to the biological reference product or modifying the amino acid sequence of the protein.⁴⁵⁻⁴⁸ In recent years, the magnitude of development of biobetters rivals that of biosimilar development.⁴⁹

Confusion surrounding biosimilars, biologics, and biobetters can be expected, particularly with the lay public. Potentially adding to the confusion is that biopharmaceutical manufacturers that develop reference biological products often develop biosimilars of competitors’ products and biobetters of their own products (Table 2⁵⁰). Improving on their own product is a typical part of the

product development cycle that can extend market share while also improving efficacy.⁴⁵⁻⁴⁸ The competition for market share may lead to innovations that distinguish products from those of competitors.

Conclusions

Biosimilars will become more prevalent in clinical practice, including in the area of oncology. This overview of the various clinical, manufacturing, and cost considerations surrounding biosimilars provides a foundation for clinicians to advance their understanding of this class of drugs. Building on this foundational knowledge, HCPs will be able to incorporate biosimilars into their practices in ways they deem most appropriate for their patients. The pipeline for biosimilars continues to expand in the United States, although, as seen with bevacizumab-awwb and trastuzumab, market availability may lag after FDA approval. By preparing for the influx of biosimilar products, HCPs will continue to provide safe and effective patient care while keeping an eye on cost considerations. ■

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