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Biosimilars: The US Regulatory Framework*

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Abstract

With the passage of the Biologics Price Competition and Innovation Act of 2009, the US Food and Drug Administration established an abbreviated pathway for developing and licensing biosimilar and interchangeable biological products. The regulatory framework and the technical requirements of the US biosimilars program involve a stepwise approach that relies heavily on analytical methods to demonstrate through a “totality of the evidence” that a proposed product is biosimilar to its reference product. By integrating analytical, pharmacological, and clinical data, each of which has limitations, a high level of confidence can be reached regarding clinical performance. Although questions and concerns about the biosimilars pathway remain and may slow uptake, a robust scientific program has been put in place. With three biosimilars already licensed and numerous development programs under way, clinicians can expect to see many new biosimilars come onto the US market in the coming decade.

INTRODUCTION

Biological products, including therapeutics, vaccines, and blood products, have been regulated in various ways by the US federal government since the early twentieth century. The last quarter of that century saw the emergence of recombinant proteins and monoclonal antibodies (mAbs), and they were also generally regulated as biological products. The scheme for regulating biological products in the United States under the Public Health Service (PHS) Act (1) differs from that for drugs, which are regulated under the Federal Food, Drug, and Cosmetic Act (2). For example, unlike a drug, a biological product is licensed under the PHS Act, and in addition the license is for the product and its manufacturing sites.

In 1984, Congress passed the Drug Price Competition and Patent Term Restoration Act (also known as the Hatch-Waxman Act) (3), which established a formal structure for generic drug regulation in the United States. However, Hatch-Waxman does not apply to biological products. This is because, for many decades, it was not deemed feasible to produce near-copies of biological products. Vaccine performance was highly dependent on manufacturing conditions; recombinant proteins and mAbs were challenging to manufacture and control; and regulators were cautious about accepting manufacturing or site changes proposed by the companies. However, by the turn of the twenty-first century, experience with these products and advances in analytical methods signaled the possibility of creating an abbreviated pathway to market for products that were close to identical to a licensed biological product. The idea of an abbreviated pathway for biological products was of great interest to legislators and government officials because biotechnology products are among the most expensive pharmaceuticals, and governments worldwide have an interest in managing healthcare costs.

In 2004, the European Union (EU) amended a directive (4) establishing an abbreviated pathway to market for similar biological medicinal, or “biosimilar,” products. The European Medicines Agency (EMA) was charged with setting up the regulatory plan and regulating these products. Since that time, many biosimilar products have come onto the European market (5).

In the United States, after several years of debate, on March 23, 2010, Congress passed the Biologics Price Competition and Innovation (BPCI) Act of 2009 as part of the Patient Protection and Affordable Care Act (6). The BPCI Act amended the PHS Act, establishing a pathway to market for biosimilar products in the United States. Congress charged the US Food and Drug Administration (FDA) with implementing a regulatory framework around the statutory provisions. Two years later, a user fee program was signed into law, permitting FDA to assess fees for the consultations and regulatory review required to conduct the program. To date, FDA has licensed three biosimilar products, and with a number of active development programs ongoing, clinicians should expect to see many biosimilar products appearing on the US market over the coming decade. This article describes the regulatory framework and technical requirements for these products in the United States, presents an overview of FDA’s approach to assessing biosimilarity, and describes some current challenges and controversies surrounding biosimilar products.

BIOSIMILARS ABBREVIATED PATHWAY

The BPCI Act created an abbreviated licensure pathway under section 351(k) of the PHS Act for a biological product to be licensed by FDA as biosimilar to, or if it meets an additional standard, interchangeable with, an already FDA-licensed reference product. A reference product (sometimes referred to as an originator product) is an already licensed biological product that the proposed biosimilar or interchangeable product is being compared to in an application. Reference products are licensed (or approved) by FDA under Section 351(a) of the PHS Act, on the basis of their stand-alone development—i.e., full dossiers of preclinical and clinical data demonstrating that the products are safe, pure, and potent.

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“Biosimilarity” is defined in the BPCI Act to mean that the “[biosimilar] biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and that there are “no clinically meaningful differences between the [biosimilar] biological product and [its] reference product in terms of safety, purity and potency of the product” (6, H.R. 3590 p. 687). “Interchangeability” is defined in the BPCI Act to mean that the “[interchangeable] biological product is biosimilar to the reference product, and it can be “expected to produce the same clinical result as the reference product in any given patient.” In addition, “for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the [interchangeable] product and its reference product is not greater than the risk of using the reference product without such alternation or switch.” The BPCI Act states that an interchangeable product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product” (6, H.R. 3589 p. 697). The abbreviated licensure pathway developed for biosimilar and interchangeable products is possible because developers of such proposed products can rely for licensure on, among other things, publicly available information from FDA’s prior determination that the reference product is safe, pure, and potent.

As already noted, biosimilar products are not generic drugs, and the data package required to support FDA’s licensure of a biosimilar product differs from that of a generic drug. An abbreviated pathway for the approval of generic drugs (typically small-molecule products) was established by the Hatch-Waxman Act for drugs that can be shown to have the “same” active ingredient as, and are “bioequivalent to,” an FDA-approved drug (3, 98 STAT. p. 1585–86). Because of the inherent complexity of biological products and their manufacturing processes, there will be lot-to-lot variability of any given biological product, and two biological products are highly unlikely to be identical, although they can be determined to be structurally and functionally highly similar. This scientific difference is the key reason for the creation of a separate abbreviated approval pathway for biosimilar biological products.

The goal of a biosimilar development program differs substantially from a program to support a stand-alone, or originator, biological product. The goal of stand-alone development is to demonstrate that the biological product is safe, pure, and potent (i.e., “safe and effective”) for one or more identified conditions of use. The objective of a biosimilar development program is to demonstrate through the “totality of the evidence” (7) that the proposed product is biosimilar to the reference product. The developer (or sponsor) of the proposed biosimilar product does not have to independently establish the safety and effectiveness of its product; it establishes this through a demonstration of biosimilarity to the reference product. Although the data packages differ, the standard for approval of originator products under 351(a) and biosimilar products under 351(k) of the PHS Act is the same, in that both must demonstrate that they are safe, pure, and potent for the approved conditions of use. Although the data package required for approval of a biosimilar product is extensive, the approval pathway is abbreviated. For example, it allows the extrapolation of data supporting biosimilarity across indications, so with adequate scientific justification, a sponsor would not need to conduct a clinical study to support approval of a biosimilar for each indication in the reference product’s label.

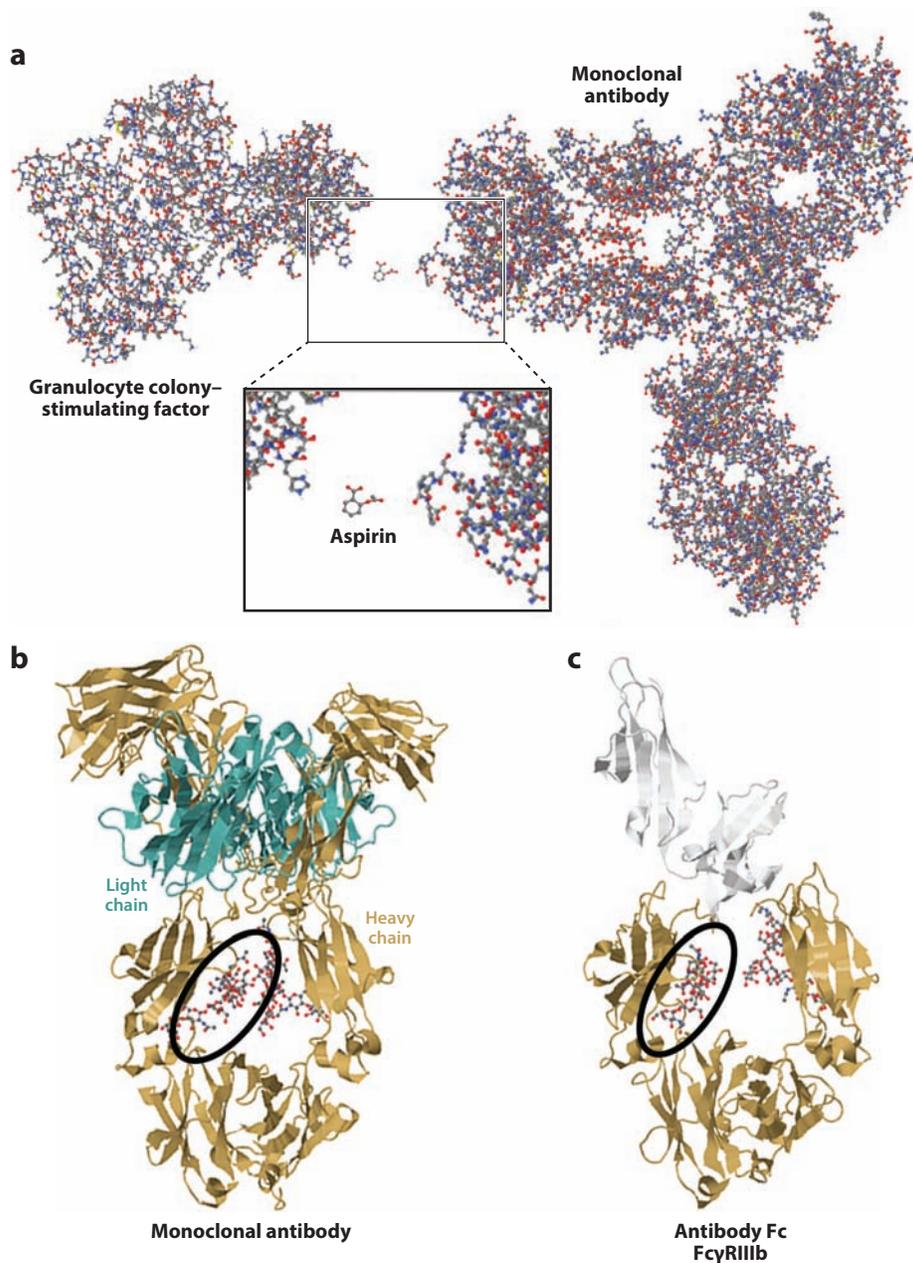
BIOLOGICAL MOLECULES: COMPLEXITIES AND UNCERTAINTIES

Size Makes a Difference

Biological molecules are generally larger and more complex than small-molecule drugs. For example, therapeutic proteins, a type of biological product, consist of a large string of amino acids that are folded in three-dimensional space. There may be many modifications to the amino acids, such



as chemical changes and additions of sugar molecules. An example of the differences in size and structural complexity between a small molecule and therapeutic proteins is shown in **Figure 1a**. A therapeutic protein product can also consist of a mixture of many molecules with slight variations in structure. The activity of a protein depends on the folding of the protein in three-dimensional space. Protein folding is illustrated in **Figure 1b** with a ribbon diagram of the same antibody shown in **Figure 1a**. The folding of proteins, also called higher-order structure, can be affected by changes in formulation and can be very sensitive to environmental conditions (e.g., temperature).



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Biological products are manufactured in living systems (e.g., in a microorganism or in animal cells). As a result, there are additional risks from impurities, contaminants, and adventitious agents, such as viruses. Thus, manufacturing processes can introduce variability into biological products that needs to be carefully controlled.

Manufacturing and Quality Assurance

Despite these challenges, biological products have a long history as pharmaceuticals. Recombinant products have been marketed as therapeutics since the early 1980s, and the use of these products has dramatically increased over time. Industry has gained a great deal of experience in developing and manufacturing these products, and regulatory agencies have gained a great deal of experience in their oversight.

Ensuring high-quality biological products is based on a multilayered control strategy that includes process design, process and facility controls, process verification, and product testing. FDA oversight of biological products includes review of the marketing application, review of any major manufacturing changes, and inspection of manufacturing sites. There is no difference between a reference product and a biosimilar product in terms of the extensive expectations for manufacturing and quality assurance (6, 8). These shared expectations for both originator and biosimilar biological products mitigate the risks of product variability, instability, and contamination.

Analytical Tools and Biotechnology Products: A Coevolution

Analytical tools have played a critical role in the development and quality assurance of biological products, and there has been a coevolution of products and analytical methods. Analytics have gone from fuzzy bands on acrylamide gels to highly specific patterns linked to protein sequence and structure. Peptide mapping (9, 10), a technique combining enzymatic digestion with high-performance liquid chromatography, was an important advance. In 2002, the Nobel Prize in chemistry was awarded for applying advanced analytical methods, mass spectrometry, and nuclear magnetic resonance (NMR) spectroscopy to the study of large molecules (11). These methods continue to grow in sensitivity and resolution. NMR has been recently used to compare different filgrastim products (12) and is one of a variety of methods that can measure higher-order structure (13).

Assays that measure biological activity, or bioassays, are a very important type of analytical tool (14, 15). Bioassays directly assess the biological activity of a protein product. Binding and cell-based assays are often used to assess product functionality.

Figure 1

Size and complexity of therapeutic proteins. (a) A comparison of the size and structure of two product classes approved as biosimilars in the United States to a small molecule, aspirin. Granulocyte colony-stimulating factor (PDB crystal structure 1RHG), a monoclonal antibody (PDB crystal structure 1HZH), and aspirin are shown as balls (atoms) and sticks (bonds). A portion of the panel is enlarged to better visualize the comparison to aspirin. (b) The monoclonal antibody in panel a is shown with its amino acid sequence depicted as a ribbon diagram. The larger heavy chains are in gold and the light chains are in turquoise. The sugars attached to the heavy chain are shown in a ball-and-stick diagram. (c) The lower or Fc portion of an antibody is shown binding an Fc receptor, FcγRIIIb (PDB crystal structure 1T83). The juxtaposition of the antibody sugars and the receptor is clear. For FcγRIIIa, the primary Fc receptor on natural killer cells, a difference in a single sugar can impact antibody-mediated cytotoxicity. The sugars on a single heavy chain are circled in both panels b and c. The differences in conformation may be due to the binding and/or differences in the molecules and crystallization conditions.



An entire ensemble of analytical methods is developed to evaluate a protein, with a focus on clinical performance. The analytics used for a specific product need to be based on a risk assessment (16–18) that considers potential effects on efficacy, pharmacokinetics (PK), safety, and immunogenicity. Although not every one of the myriad potential attributes is directly measured, emphasis is on the most important attributes. This approach is designed to reduce any residual uncertainties regarding protein clinical performance.

When considering the types of residual uncertainties that may remain after a thorough risk-based analytical evaluation, certain items are worth noting. For a protein product that exerts its activity through binding with one or more well-defined receptors, receptor binding and relevant measures of biological activity should limit uncertainty about efficacy to PK and tissue distribution. For such a protein, safety concerns related to exaggerated pharmacological activity should be mitigated by measurements of receptor binding, biological activity, and pharmacological activity. Of note, many biological product toxicities are due to exaggerated pharmacological activity (19). Biological products often have a clear mechanism of action, with a defined extracellular target, unlike many small molecules that enter cells and may have many more potential targets. Off-target toxicities, which for biological products are often driven by immunogenicity, are harder to predict. There are, however, product features that are known to affect the risk of immunogenicity (20–23). There are also structural features that are known to affect PK for certain classes of proteins. In the case of mAbs, FDA has approved close to 60 mAb-related products (not including Fc-fusion proteins), and many more antibodies have been evaluated in investigational studies. Thus, there is a large body of experience with and understanding about which product attributes and impurities could affect PK and immunogenicity.

The mechanism of action of a mAb product can include effector functions in addition to binding the target. The importance of effector functions in clinical performance depends on the nature of the target and the likely mechanism(s) of action (24). Antibodies have chains of sugars attached to the antibody heavy chain that can affect PK and effector functions (25, 26). The impact of the sugar fucose on the antibody-dependent cytotoxicity of target cells by certain effector cell types (27) is one example of how glycosylation can affect antibody function. The interaction of an antibody fragment with a receptor that mediates effector function and the spatial relationship to antibody sugars are illustrated in **Figure 1c**. This large knowledge base has further reduced residual uncertainties in clinical performance when an antibody is characterized by an appropriate ensemble of analytical methods.

Trusting Analytics to Inform Clinical Performance

A key factor in the success of originator biological products has been the ability to make changes to the manufacturing process without the same extensive data package required for initial approval. For more than two decades, clinicians have been prescribing biological products that have had their clinical performance assessed through analytical comparability evaluations (28, 29). European data on originator mAbs and Fc-fusion proteins with rheumatological indications showed as many as 37 manufacturing changes for a single originator product (30). The large body of science concerning comparability is relevant (31–33) to demonstrating that products are highly similar, a key component of biosimilarity. FDA has a great deal of regulatory experience with the application of this science, as described in a historical perspective (34), and that experience has continued to grow.

An originator biological product being prescribed today is likely to have had manufacturing changes that were evaluated by analytical methods in the absence of clinical data. Knowingly or unknowingly, clinicians and patients have relied on analytical studies, not clinical studies, to support continued safety and efficacy. Nevertheless, most prescribers are used to evaluating newly

introduced drugs based on the results of clinical trials evaluating safety and effectiveness. The new framework for biosimilarity thus creates concern. However, comparative clinical trials, though reassuring, are generally less sensitive to change than the analytical methods described above. The integration of analytical, pharmacological, and clinical data, each of which has limitations, provides a high level of confidence regarding clinical performance.

DETERMINING BIOSIMILARITY

There is no single, pivotal study that demonstrates biosimilarity. FDA intends to consider the totality of the evidence from comparative analytical, nonclinical, and clinical studies in considering biosimilar applications (7). Biosimilarity can be demonstrated using a stepwise approach, whereby residual uncertainty regarding biosimilarity is evaluated at each step. The foundation of the data is extensive structural and functional characterization of the proposed biosimilar product in comparison to the reference product to demonstrate that the products are highly similar.

To evaluate similarity, the products are compared using a risk-based set of analytical methods that cover primary structure, glycosylation, other amino acid modifications, heterogeneity in size and charge, biological activities, and higher-order structure (8). Any remaining uncertainty after this comparison is considered in subsequent steps of the evaluation. The analytical comparison may reveal a difference that is major enough to preclude a finding of “highly similar,” in which case, neither nonclinical nor clinical data will be sufficient to support a demonstration of biosimilarity. Alternatively, the data could demonstrate a slight difference in a glycosylated form of the product that may affect PK. Such a biosimilar candidate could still meet the expectation of “highly similar” if the uncertainty is mitigated by the results of a study assessing PK similarity between the proposed biosimilar and the reference product. The potential impact of the results of such an analytical similarity assessment on further expectations for product development reinforces the importance of a stepwise development of biosimilars that starts with analytics.

Clinical studies that assess PK and, if appropriate, pharmacodynamic (PD) similarity and comparative immunogenicity are important components of a demonstration of biosimilarity (7). Studies that evaluate PK and/or PD are generally considered the most sensitive clinical assays for assessing differences between products, should they exist. Nevertheless, in some cases, a comparative clinical study may be needed to further assess whether there are clinically meaningful differences between the products.

The objective of comparative clinical pharmacology studies is to evaluate the similarity in PK and PD between the proposed biosimilar product and the reference product. PK and PD similarity data can lead to a conclusion that similar exposure (and PD response, if applicable) will provide similar efficacy and safety (i.e., an exposure–response relationship exists) (35). An example of this approach is the development program for the first FDA-approved biosimilar product under the 351(k) pathway, Zarxio[®] (filgrastim-sndz), where clinical pharmacology studies evaluated PK similarity and a comparative assessment of absolute neutrophil counts and CD34⁺ cell counts as relevant and sensitive PD markers to support a demonstration of “no clinically meaningful differences.” However, relevant PD biomarkers may not always be available.

Although some structural attributes are known to affect immunogenicity, immunogenicity cannot currently be predicted for complex protein products solely using analytical methods. As a scientific matter, a study assessing immunogenicity is generally expected (7). An immunogenicity study should evaluate potential differences in immunogenicity that could lead to a clinically meaningful difference between a proposed biosimilar and reference product. Often this can be done as part of another clinical study; however, there may be situations when a study specifically designed to evaluate immunogenicity is needed.



If needed, comparative clinical studies should be designed to investigate whether there are clinically meaningful differences in safety and efficacy between the proposed biosimilar and the reference product. It is not scientifically necessary for the primary endpoint in a comparative clinical study to be the same as the endpoint used to demonstrate efficacy of the reference product. The study population, endpoints, sample size, and duration should be adequately sensitive to detect any differences between the products.

A biosimilar product can be approved for one or more conditions of use for which the reference product is licensed based on extrapolation of clinical data intended to demonstrate biosimilarity in one condition of use. The sponsor of a proposed biosimilar product needs to provide sufficient scientific evidence to justify extrapolating data (7).

REMAINING QUESTIONS

A number of questions remain with regard to biosimilars. For example, what types of data and information will be needed for a biosimilar biological product to be considered interchangeable? How should biosimilar products be named and labeled to prevent confusion and promote safe use?

Interchangeability

Healthcare practitioners can prescribe biosimilar and interchangeable biological products just as they would prescribe other medications. If a biosimilar product can meet the additional standard to be licensed as an interchangeable biological product, it can be substituted for the reference product by a pharmacist without the intervention of the prescribing healthcare practitioner (6). In contrast, FDA expects that a biosimilar product that has not met the additional standard would be prescribed by a healthcare practitioner and would not be substituted for a reference product at the pharmacy level. As an aid, FDA has posted its *Purple Book*, which provides information on whether a biological product has been determined by FDA to be biosimilar to, or interchangeable with, a reference product (36).

FDA is carefully considering the type of data and information needed to meet the standard for interchangeability. There are many stakeholder views on the expectations for interchangeability. It is important that the expectations are both feasible and scientifically robust in supporting pharmacy-level substitution of biological products.

Naming

A great deal of discussion has centered on the naming of biosimilar biological products. Would distinctive nonproprietary names for biological products minimize inadvertent substitution? Should interchangeable biological products share a nonproprietary name with their reference product? The naming convention ultimately chosen should enable safety surveillance for all biological products. FDA has solicited input on a final approach to naming and will consider all of these issues as part of the naming decision process (37).

Labeling

A biosimilar product is not required to have the same labeling as its reference product, and biosimilar product labeling may differ from the reference product labeling for a variety of reasons.

For example, a biosimilar product may not be approved for all the indications for which the reference product is approved (38).

As noted, comparative clinical studies in a biosimilar development program are intended to demonstrate that there are no clinically meaningful differences between the proposed biosimilar and the reference product. However, comparative clinical studies may use design parameters that differ from those used to support the approval of the reference product. Although necessary for FDA to make a decision about biosimilarity, these comparative data are not likely to be relevant or informative to a healthcare practitioner's prescribing considerations. In fact, because of the potential for differences in clinical study parameters, FDA has stated that including such data in biosimilar product labeling could be confusing, even misleading, to healthcare practitioners. FDA's draft guidance development process provides an opportunity for stakeholders to comment on FDA positions, and FDA will consider comments on this topic as part of the labeling decision process (39).

BARRIERS TO UPTAKE IN THE UNITED STATES

Biosimilars will provide savings to patients and healthcare plans only to the extent that they are prescribed. Although US clinicians and patients are very interested in more affordable biological products, many have voiced concern and uncertainty about the performance of this new class of products. In contrast, European clinicians, who have quite a few years of experience with marketed biosimilar products, indicate more comfort with using them (40). Today, generic drugs constitute >85% of dispensed prescriptions in the United States, but this level of acceptance took many years to achieve.

Multiple factors may influence uptake of biosimilar products in the US market. Prescriber experience with generics and confusion between generic drugs and biosimilars could slow US uptake of biosimilars. Approval as a biosimilar means that the biological product can be prescribed for an individual patient but should not be substituted at the pharmacy level, whereas approval of an interchangeable allows such a substitution. FDA's *Purple Book* will help prescribers as they make prescribing decisions. However, the kind of serial substitution that currently occurs with generic drugs, where multiple substitutable products are marketed, is unlikely to occur with biological products in the foreseeable future.

Many patient and physician groups have indicated that biosimilar products should be clearly identifiable, so that users are immediately aware of what product is being administered. Prescriber groups have indicated that package inserts should clearly identify the product as a biosimilar or interchangeable product. FDA's draft labeling guidance recommends that this information be included in the package insert and suggests a standard placement. The draft guidance also calls for language explaining the concept of biosimilarity (38). The three biosimilars approved to date have designated brand names; however, FDA cannot mandate that drugs have brand names. The Agency has proposed distinguishable nonproprietary names for biological products, including biosimilar products, to facilitate administrative tracking, for example, to monitor possible adverse events.

Clinicians have also expressed concern about the amount of clinical data that will be generated to support the approval of a biosimilar. The clinical community is very familiar with new drug development, wherein drug approvals are supported by adequate and well-controlled clinical trials in each indication studied and approved. This is not the paradigm for biosimilars. The types of intensive analyses that are performed to support a finding of biosimilarity are generally more sensitive to product differences than reasonably sized noninferiority trials. This concept has taken a while to be understood both within FDA and in the drug development community. The clinical



practice community will likely continue to have similar concerns over the next few years, especially when extrapolation of clinical data in one indication to additional indications is done without head-to-head clinical studies. Such concerns may well slow biosimilar uptake for specific populations.

Finally, it is likely that legal challenges will occur during the early years of implementation of the US biosimilars program. Litigation has been a common feature of FDA's generic drug review program. A provision in the BPCI Act provides for information exchange between biosimilar applicants and the reference drug sponsor, and litigation is currently ongoing in this area. Legal challenges could delay availability of certain biosimilar products.

Improved versions of biological products or "biobetters" have and will continue to be developed (41). Biosimilar competition could impact development of such biological products. Biosimilars will also lead to innovations in analytical methods and clinical evaluations. These advances may also enhance the development of new originator biological products.

THE FUTURE IS BRIGHT

Despite these questions and concerns, a robust US program is in place for the licensure of biosimilar biological products. With three biosimilar products already licensed and multiple development programs under way, it is clear that biosimilars will become a reality in the United States. Nevertheless, the growth rate of market availability is difficult to predict, as is the number of competitor products that will be available for any given biological product. Continuing advances in analytical science and increasing clarity of regulatory requirements will improve predictability for industry. Clinical experience with biosimilars should ease the concerns of prescribers and patients. The next decade should bring the widespread availability of safe and effective biosimilar options for many diseases and conditions.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. Readers interested in the specifics of biosimilar development should consult FDA guidances.

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