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Special REPORT

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,

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biologics are much larger and inherently more complex products produced in living systems (Table 1).[2,9] Because of this, similar but not exact copies are possible, called biosimilars.[2,9]

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.[9,20] 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.[9]

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.[21]

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.[22] 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).[22] 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.[22]

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

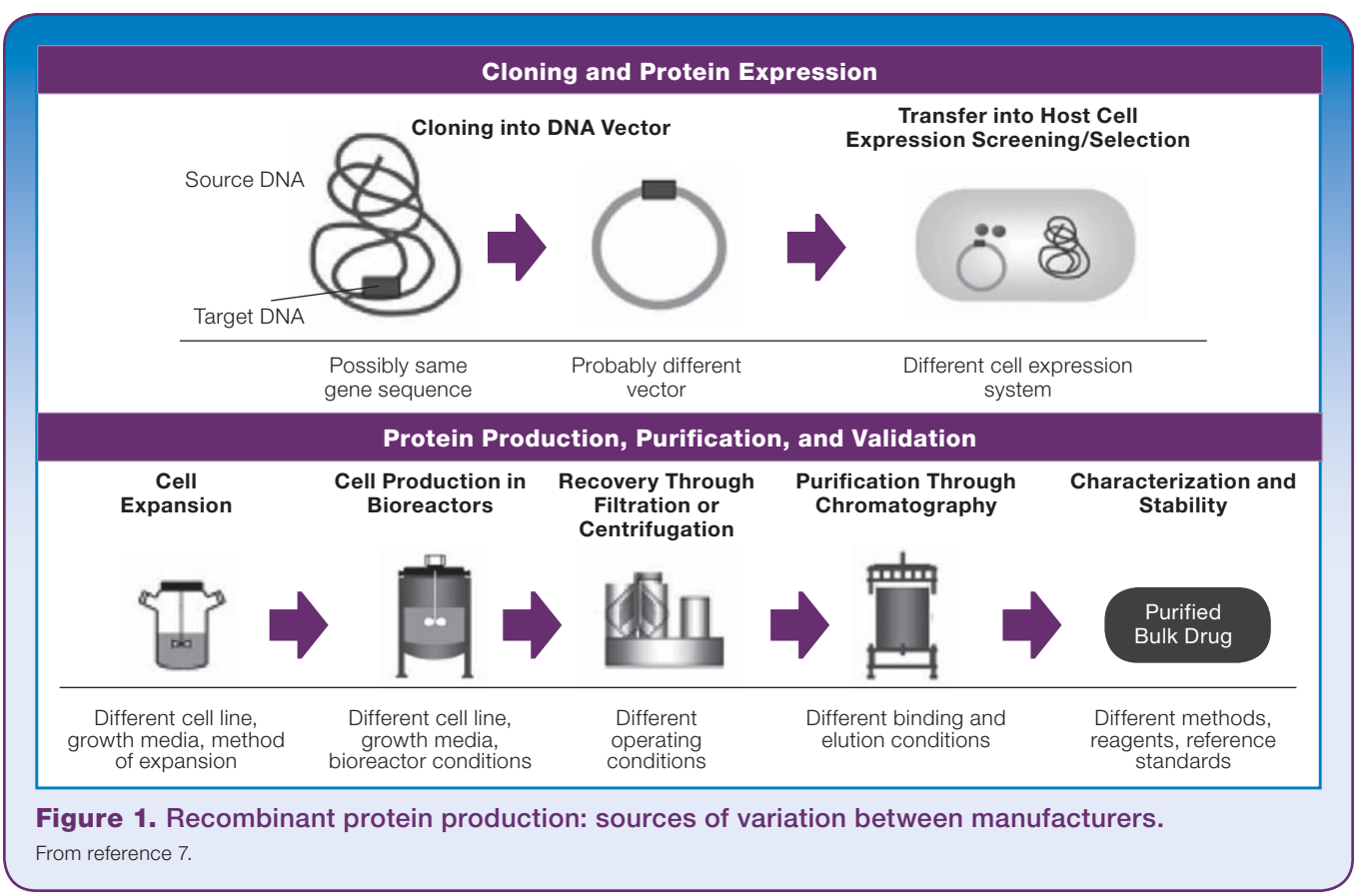

Figure 1. Recombinant protein production: sources of variation between manufacturers.

From reference 7.

the likelihood of recouping up-front R&D costs.[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."[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.[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.[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.[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.[29] The second guideline addressed quality issues (physiochemical properties, biological activity, and purity), and the third described nonclinical and clinical issues.[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.[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.[32,33]

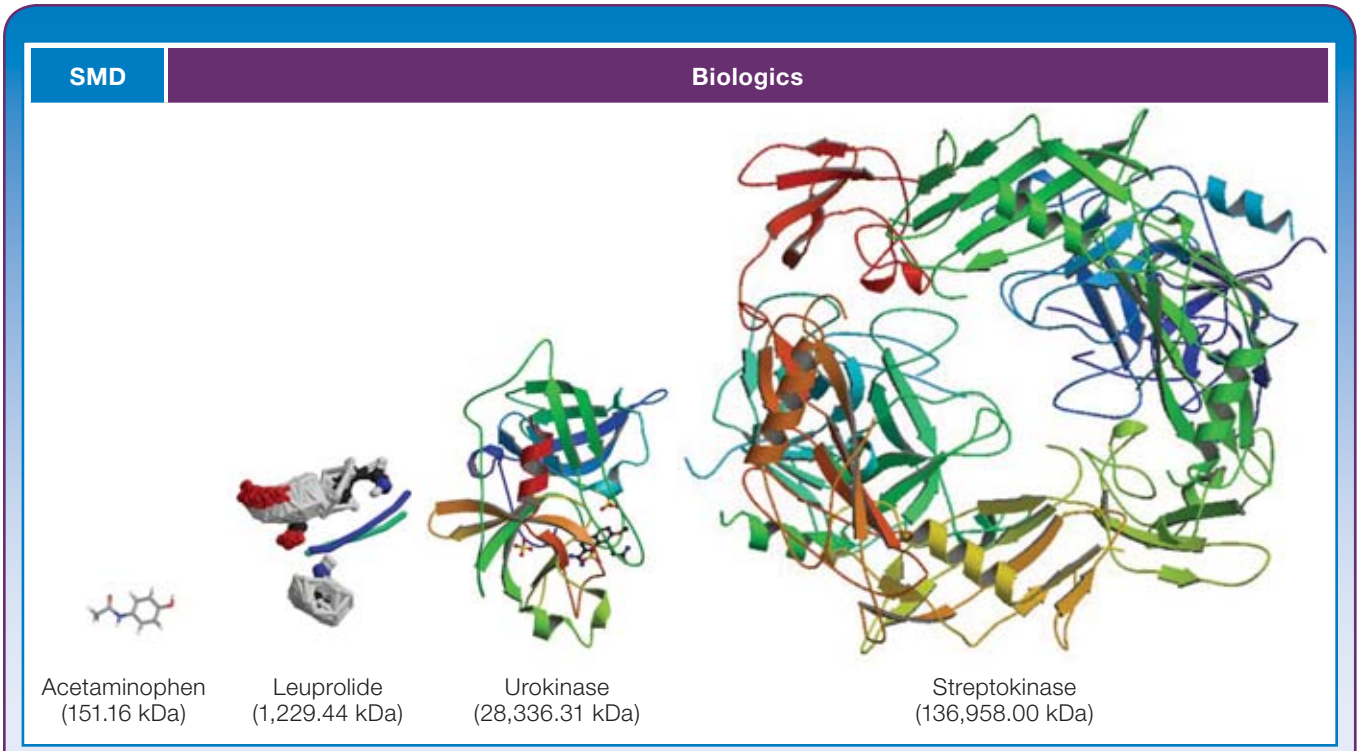

Figure 2. Comparative molecular weights of representative biologics and SMDs.

SMD, small molecule drug

Adapted from references 13-19.

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

Feature	Small Molecule Drug	Biologic Agent
Example	Acetylsalicylic acid (180 Da)	Monoclonal antibody (~150,000 Da)
Entity	Chemical	Protein
Structure	Small, simple, well characterized	Large, complex, heterogeneous
Stability	Stable	Unstable
Mode of administration	Usually amenable to ingestion	Usually requires injection or infusion
Manufacturing process	Predictable and precise method; identical copies in batches	Living cell-based complex technology; batch-to-batch variation, sensitive to storage and handling
Immunogenicity	Mostly nonimmunogenic	Immunogenic

Adapted from references 2 and 9.

The European framework has helped to guide thinking about requirements and issues for creating a pathway elsewhere in the world, including Korea, Japan, and Canada.[34]

World Health Organization

The World Health Organization (WHO) plays an active role in fostering the development of regulatory guidelines for therapeutic agents in the interest of standardization of data requirements, thereby decreasing barriers to the international use of beneficial drugs. In doing so, the WHO issued guidelines for the evaluation of biosimilars (called Similar Biotherapeutic Products [SBPs] in its terminology) in October 2009, with a view toward ensuring better access to safe and effective SBPs worldwide through global harmonization of the regulatory framework for licensure.[35]

This guideline describes a stepwise approach, starting with characterization of quality attributes of the product, followed by nonclinical and clinical evaluations. The WHO guidelines indicate that manufacturers should submit a full quality dossier that includes a complete characterization of the product, the demonstration 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 marketing 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 similar 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 jurisdictions. The law defines interchangeable to mean that the biosimilar product may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.[37,39] Once approved, most generic drugs can be substituted automatically for the reference product without the intervention of the healthcare provider 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 interchangability designation, a product is first determined to be a biosimilar, and then may be considered for a determination of interchangability with the reference product. Determination of interchangeability not only requires demonstration of biosimilarity, but also that the product is expected to produce 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 developing biosimilar products.[26] The abbreviated Biologic License Application pathway guidance consists of 3 documents, one each covering the scientific and quality considerations in demonstrating 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 Biosimilarity to a Reference Protein Product," and "Biosimilars: Questions 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

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

Issue	Requirements
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 proposed for the biological product has been previously approved for the reference product.
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.

applications for biosimilars, including the robustness of the manufacturing process; the demonstrated structural similarity; the extent to which the mechanism of action was understood; the existence of valid, mechanistically related pharmacodynamic (PD) assays; comparative pharmacokinetics (PK) and immunogenicity, and the amount of clinical data and experience available for the reference products.[41]

The FDA draft guidelines also are similar to those issued by the WHO in that they recommend a stepwise approach to establishing the comparability of the original biologic and its proposed biosimilars. This approach should begin with an extensive structural and functional characterization of the proposed biosimilar product and reference product. The more comprehensive and robust this characterization, the more useful such characterization will be in determining what additional studies may be needed. The sponsor should then consider the role of animal data in assessing toxicity as well as providing additional support for demonstrating biosimilarity. Comparative human PK and PD studies should be conducted in an appropriate population along with a consideration of the clinical immunogenicity to evaluate the potential incidence and severity of human responses. At each step, sponsors should assess the extent to which there may be residual uncertainties about the proposed biosimilarity and identify ways to address that uncertainty.[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.[41] 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.[41]

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.[37,41]

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.[42,43] 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.[36] 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.[44]

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.[45,46] Thus, while the FDA continues to consider

what type of information ultimately will be required to demonstrate interchangeability, manufacturers seeking an interchangeable designation for their biosimilar product likely will be required to provide a higher level of data than for a biosimilar approval without an interchangeable desgination.[45,46] 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 determine 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, manufacturers, and regulatory bodies. Until that time, collection of accurate 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 voluntary 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 identify and report the associated product. A robust post-approval safety surveillance program will have to include precise AE tracking and tracing capabilities to detect and evaluate potential safety 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 nonproprietary name as the innovator product. The challenge of biosimilars 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 formulary 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 surveillance 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 evaluate 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 framework 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 definitively 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 professionals with regard to regulatory pathways; a survey of 277 physicians, nurses and pharmacists, and other clinicians conducted 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 surrounding biosimilars, a fact that points to the necessity of education 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 pharmacists 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 biosimilar regulatory process, with the goal of assuring that patients have access to safe, effective, and less expensive biologic therapies. 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 efficacy 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 formulary 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.

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