CHAPTER

# 6

# Regulatory Standards for the Approval of Biosimilar Products: A Global Review

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## INTRODUCTION

Various terms have been used in different regions of the world for copies of innovator biological (biotechnology-derived) protein therapeutics (or biologics, which is the term that will be used hereinafter), such as similar biological medicinal products (Europe and Australia), subsequent entry biologics (or SEB; Canada), and in the United States, follow-on biologics (or FOB), and biosimilars. Biosimilar is the most widely accepted term for copies of biologics, and will be the term used in this chapter. A biosimilar is a "follow-on" or copy version of an innovator biologic therapeutic product (e.g. monoclonal antibodies, recombinant proteins, fusion proteins) that has already been approved by a regulatory authority and marketed [1].

Data exclusivity and patents represent complementary forms of intellectual property for innovative products that have expired or will expire soon [2]. A patent is granted for innovative products based on the criteria of novelty and utility, and generally has a term of 20 years from the filing date of the application in the United States [2]. The data exclusivity (also called data protection period), which varies across regions (e.g. 12 years in the United States; 10 years in Europe), is the period of time after a new product is approved before an imitator or copy product can rely on the innovator's safety and efficacy data for approval and enter the market with an abbreviated regulatory filing [2–4]. At this writing (2013), the data exclusivity and the patent protecting many innovator biologics have expired or will soon reach expiration, and consequently, many biopharmaceutical manufacturers are working to develop and market copies of these innovative products.

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As described in Chapter 7, fundamental differences exist between traditional, small-molecule (chemical) pharmaceuticals and biological products. In comparison to small-molecule products, biologics are significantly more complex in structure and physiochemical properties [5–7]. Legislators and regulatory authorities around the world acknowledge the substantial differences between small-molecule products and biologics, and, as a result, recognize that the regulatory pathways for the approval of copies of small-molecule medicines (generics) are not scientifically appropriate for biosimilars [8–10].

Generic medicines contain the identical active substance(s) as the reference product [11–13]. As such, the regulatory standards for the approval of generics are predicated on the demonstration of sameness between the generic and reference product [8,9]. Generic medicines demonstrated through comparative analytical tests to be pharmaceutically equivalent to the reference product are considered to be therapeutically equivalent to a reference product. The requirements for generic medicines to gain market approval generally have been limited to comparative analytical tests and demonstration of clinical bioequivalence (i.e. absorbed into the body at an extent and rate similar to the reference product), and these tests typically are conducted in healthy volunteers. Thus, clinical efficacy and safety studies are generally not necessary for the approval of generic medicines [3,9,14–18]. The presumption that a generic product has an efficacy and safety profile equivalent to the reference product is based on the demonstration of pharmaceutical equivalence (through comparative analytical tests) and clinical bioequivalence. However, unlike generic medicines, the active substance of a biosimilar is similar, but not identical, to that of the reference product, and therefore cannot be pharmaceutically equivalent to the reference product [16,19].

Inherently, there will be differences in some product attributes between a proposed biosimilar and the reference product, and while minor differences are acceptable, evidence must be provided that these differences have no impact on the product's purity, safety, or efficacy in the patient population of interest. A bioequivalence study provides exposure data for a short duration only; therefore, it is insufficient to fully determine the impact of the differences in the efficacy and safety of the biosimilar candidate in patients [1,14]. In addition, a bioequivalence study is not designed to characterize and detect "sameness" in the anti-drug antibody (ADA) responses between the proposed biosimilar and reference product because in many cases, immunogenic responses are not detected months after the biologic has been administered [14]. Therefore, demonstration of clinical efficacy and safety may be required for the approval of a biosimilar product. The need for such testing depends on various factors, including the extent to which a proposed biosimilar has been demonstrated to be similar to the reference product through comparative analytical and nonclinical studies and demonstration of clinical bioequivalence.

The regulatory standards for the approval of biosimilar products has been an area of discussion and debate for several years among the pharmaceutical industry, regulatory health authorities, and interested stakeholders, including healthcare professionals (e.g. physicians and pharmacists), third-party payers, and patient advocacy groups. In distinguishing between generic medicines and biosimilars, regulatory standards and guidelines have been established in regions around the world. Major regulatory regions, including Europe, Canada, Australia, Japan, and recently the United States, have developed distinct regulatory pathways for the approval of biosimilar products (Figure 6.1). In addition, the World Health Organization (WHO) have established guidelines for the approval of biosimilar products for national regulatory authorities considering the approval of biosimilar products in their regions [20,21].

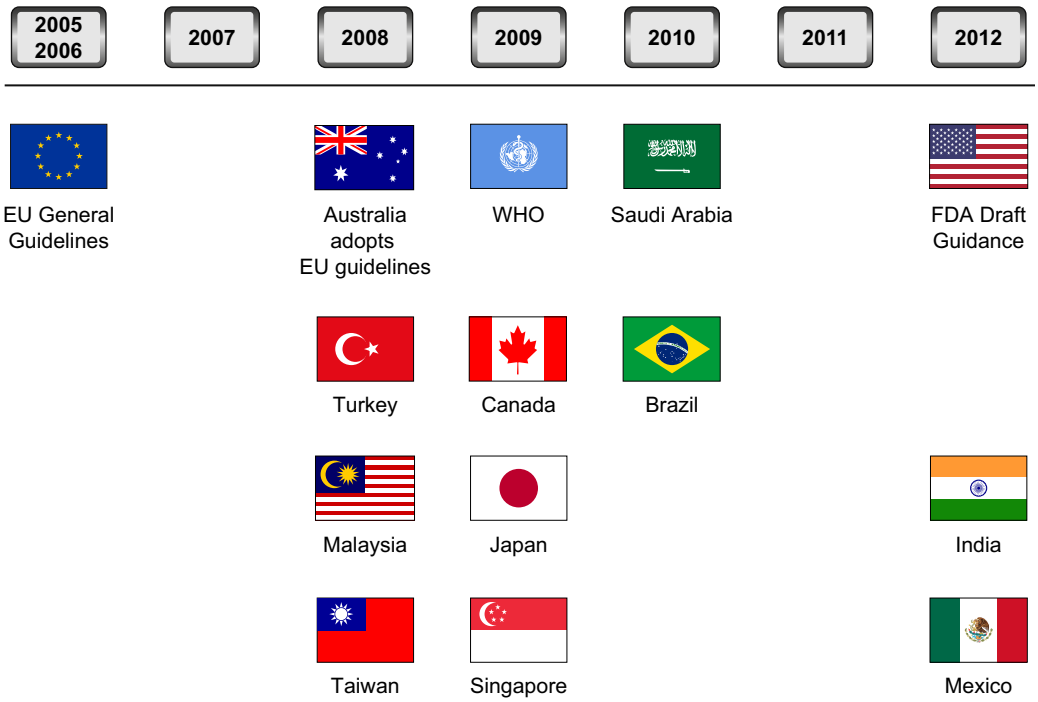


**FIGURE 6.1** Established regional regulatory pathways for biosimilar products. With the exception of the FDA guidance, dates reflect final regulatory guidance documents. *From* www.gabionline.net*; Mounho et al. [21].* Please see color plate section at the back of the book

While there are commonalities in the principles and scientific standards for the approval of biosimilar products among the various regional and WHO guidelines, key differences in certain principles and data requirements do exist, which create challenges for manufacturers of biosimilars, particularly those seeking global approval for their product [21]. This chapter reviews the history of established regulatory pathways for the approval of biosimilar products across the major regulatory regions around the world (including Europe, Australia, Canada, Japan, and the US) and summarizes some of the similarities and differences—particularly the nonclinical toxicology studies—among biosimilar guidance documents from those regions. The review also includes countries that are considered regions of rapidly growing economies ("emerging markets"), such as Brazil and India.

## EUROPEAN UNION—PIONEER FOR THE FIRST REGULATORY PATHWAY FOR BIOSIMILAR PRODUCTS

### Overview

Europe is the first highly regulated region where patents for innovator biologic products have begun to expire. Recognizing that legal and regulatory standards for generic medicines

were not suitable for the approval of an attempted copy of an innovator biologic, the European Union (EU) has pioneered the creation of a legal and regulatory framework for biosimilar products [21,22]. The European Commission (EC) established legislation for the approval of biosimilar products by enactment of an amendment to the Annex to Directive 2001/83/EC in 2003, followed by an enactment amendment to article 10(4) of directive 2001/83 in 2004, which authorized the European Medicines Agency (EMA) to oversee the approval of biosimilar products [3,21,23–25]. Subsequently, in 2005 and 2006, the EMA released three general regulatory guidelines defining the general principles and scientific standards for the approval of biosimilars:

- Guideline on Similar Biological Medicinal Products (also referred to as the "overarching" guideline) (EMEA/CHMP/437/704) [26]
- Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Nonclinical and Clinical Issues ("nonclinical/clinical guideline"; EMEA/CHMP/BMWP/42832/2005) [27]
- Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (quality guideline; EMEA/CHMP/BMWP/49348/2005) [28].

The European guidelines were generated through a consultation process within the EMA (through collaborations with various working parties), as well as externally, where the EMA received consultation from a network of various groups, including Scientific Advisory Groups, National Competent Authorities of EU Member States, and academic societies [29]. In addition, the EMA welcomed a public consultation and input from interested parties such as healthcare professionals and the pharmaceutical industry [23,29].

## "Overarching" Guideline

The "overarching" guideline defines the general concepts of biosimilarity, and specifically states that biosimilar products are "by definition" not generics, and that the approach to approval of generics is scientifically not appropriate for biosimilars [26]. Because the active ingredient of an attempted biosimilar product is not identical to the reference product, therapeutic equivalence cannot be assumed, and therefore, evaluation of clinical bioequivalence is not sufficient to demonstrate that the similar (but not identical) nature of the proposed biosimilar does not affect patient efficacy and safety [23,26,29]. In principle, the concepts of the EMA biosimilar guidelines are applicable to any biologic product. The "overarching" guideline, however, states that due to the spectrum of molecular complexity in physiochemical and functional characteristics, certain biologic products such as vaccines need to be considered on a case-by-case basis. In the case of blood or plasma-derived products, these cannot be approved based on an abbreviated clinical package when claiming similarity to a reference product; sponsors will need to provide the safety and efficacy data required by the relevant guidelines for new products [26]. The "overarching" guideline also requires that the same reference product be used across the comparability program for quality, safety, and efficacy studies during the development of a biosimilar, and that it be a medicinal product authorized by the EC on the basis of a complete dossier [26]. In addition, the "pharmaceutical form, strength, and route of administration of the proposed biosimilar should be the same as that of the reference product" [26].

## Quality Guideline

The EMA quality guideline states that in addition to a full quality dossier, a comparative analytical evaluation of the proposed biosimilar and reference product is required. The comparability exercise at the quality level is the basis for allowing a reduction of the nonclinical and/or clinical data requirements compared to a full dossier [28]. While the scope of the quality guideline includes the quality issues to demonstrate comparability of a proposed biosimilar product to a reference product, it does not address the comparability exercise to support changes in manufacturing processes that occur during the development and/or post-authorization of a given product. Regarding issues relating to manufacturing process changes, the guideline refers applicants to the appropriate guidance (e.g. ICH Q5E). The quality guideline acknowledges that minor differences in quality attributes (e.g. variability in posttranslational modifications) and impurity profiles will exist between the proposed biosimilar and reference product, and while such differences may be acceptable, a stepwise approach to investigate, identify, and quantify the differences should be used to provide sufficient justification for the potential impact of the differences on clinical safety and efficacy [28]. The analytical methods used for the comparative analysis should be state of the art, and the sponsor is responsible for demonstrating that the methods selected "would be able to detect slight differences in all aspects pertinent to the evaluation of quality." The comparability exercise should include the evaluation of physiochemical parameters (e.g. composition, primary and higher order structures of the active substance) and biological properties, using distinct, appropriate assays to measure biological activity. In addition, the comparability exercise should include a comparison of the proposed biosimilar and reference product stability profiles, and degradation should be assessed by performing stress and accelerated stability studies; the purity and impurity profiles of the active substance and medicinal product should be assessed qualitatively and quantitatively using a combination of analytical procedures for both the proposed biosimilar and the reference product [28].

## Nonclinical and Clinical Guideline

The nonclinical/clinical guideline addresses the general principles for the nonclinical and clinical data required to demonstrate similarity between a proposed biosimilar and innovator biologic product [27]. The nonclinical studies should be performed before initiating clinical trials, and they should be comparative in nature (i.e. head-to-head comparison study with the proposed biosimilar and reference product), and "tailored to the specific product concerned on a case-by-case basis." Based on the existing nonclinical/clinical guideline, the nonclinical program may include *in vitro* studies (e.g. receptor binding or cell-based functional assays) and/or *in vivo* studies. The animal studies should be designed to detect differences in the measured response (e.g. pharmacological or toxicological effects), and at least one repeat-dose toxicity study should be conducted, including toxicokinetics (TK) and measurement of ADA responses; this study should be of sufficient duration to detect relevant differences in toxicity and/or immunogenicity responses [27].

Other routine toxicological studies (e.g. safety pharmacology, reproductive toxicology, and carcinogenicity) are generally not required unless data from the repeat-dose study indicated

that they are warranted. The type and extent of clinical studies required depend on various factors, including the complexity of the active substance and how well it can be characterized, what is known about the reference product and the claimed indications, the type and seriousness of adverse events encountered with the reference product or product class, and availability of an accepted surrogate endpoint to compare efficacy [27]. The guideline recommends a stepwise approach be applied to the clinical comparability exercise, starting with clinical pharmacokinetic (PK) and pharmacodynamics (PD) studies, followed by efficacy and safety studies [27]. The clinical PK study(ies) should be comparative, and the study design (e.g. single vs. repeated dose) must be justified by the applicant based on the specific characteristics of the reference product (e.g. long half-life or high immunogenicity profile). If available, biomarkers of the PD effect should be incorporated into the PK study design and evaluated where potential differences between the proposed biosimilar and reference product can best be observed because combined PK/PD studies may provide "useful information on the relationship between exposure and effect [27]." In some cases, comparative PK/PD may be "sufficient to demonstrate clinical comparability," given that the margins defining clinical comparability of PK and PD parameters are justified and predefined, and that certain conditions are met:

- The PK of the reference product is well characterized.
- The PD properties (e.g. receptor binding, mechanism of action) and the dose/exposure and response/efficacy relationship (therapeutic "concentration–response" curve) of the reference product are well characterized.
- At least one PD endpoint is an acceptable surrogate marker for clinical efficacy and the relationship between dose/exposure to the reference product and PD markers of the primary endpoint (to measure efficacy) is well characterized.

Comparative clinical trials will generally be necessary to demonstrate comparability between the proposed biosimilar and reference product [27]. Clinical safety data are also required for approval, and the type, severity, and frequency of the adverse events between the proposed biosimilar and the reference product should be compared. Clinical studies are usually insufficient to identify all of the potential differences in the safety profile between the proposed biosimilar and reference product; therefore, sponsors are generally required to monitor the clinical safety of the biosimilar product following authorization. The applicant should provide a risk management/pharmacovigilance plan in the application dossier, and any specific safety monitoring required for the reference product (or product class) should be considered [27]. In addition to safety, clinical immunogenicity data from a sufficient number of patients are required for approval, and various factors must be considered in the applicant's strategy for evaluating immunogenicity. Such factors include the consequences of immunogenic responses (e.g. neutralization of the biosimilar's pharmacological activity resulting in reduced efficacy vs. neutralization of an endogenous protein resulting in toxicity), factors contributing to immunogenicity (e.g. process-related impurities), and the risk of immunogenicity in different therapeutic indications (e.g. patients administered immunosuppressive therapy vs. patients not administered immunosuppressants) must be considered in the applicant's strategy for evaluating immunogenicity [27].

## Product Class-specific Guidelines

While the concepts and principles presented in the general EMA biosimilar guidelines described above apply to all proposed copies of innovator biologics, there is no one standard data set (i.e. nonclinical and clinical) that can be applied to all product classes of biologic products [30]. Each class of biologics, whether a recombinant protein, monoclonal antibody, fusion protein, etc., differs in terms of mechanism of action (e.g. target mediated vs. target- and/or effector-mediated), and PK, PD, and/or PK/PD relationship. In many cases, biologic products do not have robust, sensitive PD (surrogate markers) of efficacy. In addition, biologics vary in the risk of adverse events, including the type, severity, and frequency, all of which influence the benefit/risk profile of a biologic [30].

For these reasons, the EMA developed product class-specific biosimilar guidelines, which provide detail on the nature of the nonclinical and clinical studies required in the comparability exercise based on specific properties of the reference product or product class, such as the safety/immunogenicity profile and specific endpoints for measurement of efficacy [24]. The product class-specific guidelines (those that are finalized and those currently being drafted) are presented in Table 6.1.

Monoclonal antibodies (mAbs) are established as a major product class of biological products due to structural (e.g. tertiary and quaternary structure) and functional (e.g. target- and/or effector-mediated mechanism of action) complexities [31]. MAbs may have several functional domains (depending on the isotype), including an antigen-binding region, and/or a complement-binding region, and/or an Fc receptor binding region, which account for the unique mechanism of action of each type of therapeutic mAb. Accordingly, the EMA has issued a guideline specific to biosimilar mAbs [32], which became effective in December 2012. The biosimilar mAb guideline complements the principles of the existing general guidelines. Its scope addresses issues specifically related to mAbs as well as related molecules, such as fusion proteins containing human immunoglobin Fc fragment ("cept molecules"; examples of the international nonproprietary name for such molecules are aflibercept, etanercept, and abatacept). This guideline addresses the nonclinical and clinical requirements for the demonstration of similarity for the approval of biosimilar mAbs, but does not address the quality issues (the quality issues relating to biosimilar mAbs are reviewed in the recently revised quality guideline described above). A principal concept of the guideline is that an extensive quality comparability exercise, employing state-of-the-art methods, is the foundation of the biosimilar mAb comparability program, and the nonclinical and clinical studies are meant to fill in the "knowledge gaps" of identified minor physiochemical and functional differences. The guideline reiterates that the nonclinical and clinical studies should be designed to detect any potential differences between the proposed biosimilar and reference product, as well as to determine the relevance of such differences [32].

A risk-based, stepwise approach should be applied to the nonclinical studies—the guideline recommends that *in vitro* studies be conducted first, and then it is determined whether *in vivo* studies (if any) are warranted. The *in vitro* studies should be comparative in nature, should broadly cover the functional aspects of the mAb, and should be sensitive enough to detect differences in the "concentration–activity relationship between the proposed biosimilar and reference product [32]." Examples of *in vitro* studies (some of which may be conducted as part of the comparative quality studies) include binding affinity to the target, as well as

**TABLE 6.1** EMA Product Class-specific Biosimilar Guidelines

| Guidance | Reference number | Status |
|---|---|---|
| Similar biological medicinal products containing monoclonal antibodies—nonclinical and clinical issues | EMA/CHMP/BMWP/403543/2010 | Effective December 1, 2012 |
| Draft guideline on similar biological medicinal products containing recombinant follicle stimulation hormone | CHMP/BMWP/671292/2010 | Deadline for comments on draft guideline was May 31, 2012 |
| Draft guideline on similar biological medicinal product containing recombinant interferon beta | CHMP/BMWP/652000/20100 | Deadline for comments on draft guideline was May 31, 2012 |
| Draft guideline: Revision of similar biological medicinal products containing low-molecular-weight heparins (existing guideline effective October 2009) | EMEA/CHMP/BMWP/118264/2007 Rev. 1 | Deadline for comments on draft guideline July 31, 2013 |
| Revised guideline on similar biological medicinal products containing recombinant erythropoietins (initial guideline was effective March 2006) | EMEA/CHMP/BMWP/301636/08 | Effective September 2010 |
| Nonclinical and clinical development of similar medicinal products containing recombinant interferon alpha | EMEA/CHMP/BMWP/102046/2006 | Effective April 2009 |
| Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues—Guidance on biosimilar medicinal products containing recombinant granulocyte colony stimulating factor | EMEA/CHMP/BMWP/31329/2005 | Effective June 2006 |
| Annex to guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: nonclinical and clinical issues—Guidance on similar medicinal products containing somatropin | EMEA/CHMP/BMWP/94528/2005 | Effective June 2006 |

**TABLE 6.1** EMA Product Class-specific Biosimilar Guidelines (*cont'd*)

| Guidance | Reference number | Status |
|---|---|---|
| Concept paper: Revision of the guideline on nonclinical and clinical development of similar biological medicinal products containing recombinant human insulin (existing guideline effective June 2006) | EMA/CHMP/BMWP/506470/2011 | Deadline for comments is June 30, 2013 |

*From: www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp&mid=WC0b01ac058002958c.*

binding to relevant Fc receptors (e.g. three Fcγ receptors and FcRn), Fab-mediated functions (e.g. receptor activation or neutralization of a soluble ligand), and Fc-mediated functions such as antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity).

The existing EMA biosimilar nonclinical/clinical guideline [27] states that at least one comparative repeat-dose toxicity study should be conducted (as described above). In contrast, the biosimilar mAb guideline states that *in vitro* studies can be more specific and sensitive than *in vivo* studies, and the need (if warranted), type, and extent of the animal studies should be based on the information obtained from the comparative quality and *in vitro* studies. The guideline recognizes that the effects mediated by certain mAbs in some cases cannot be fully characterized *in vitro,* and comparative *in vivo* studies may be necessary. Several factors should be considered to determine whether *in vivo* studies are necessary as part of the nonclinical comparability exercise:

- Availability of a pharmacologically relevant animal species.
- Relevant quality attributes present in the proposed biosimilar in significantly different amounts compared to those detected in the reference product or not detected in the reference product.
- Significant differences in the formulation of the proposed biosimilar versus the reference product or excipients not commonly used in mAbs.
- Whether Phase I will be conducted in healthy volunteers or patients.

If *in vivo* studies are considered to be warranted, the animal studies should be designed to obtain the maximum amount of information, and the principles of the "3Rs" (replacement, refinement, and reduction) should be taken into account (per European directive 2010/63/EU). The guideline also states that "repeated dose toxicity studies in nonhuman primates are usually not recommended." However, in cases where animal studies are warranted, a modified approach (vs. a traditional repeated-dose toxicity study), such as a non-terminal PK and/or PK/PD study, may be sufficient, depending on the endpoints that need to be evaluated [32]. In addition, while the guideline recognizes that the assessment of ADA responses in animals is generally not predictive of the human immunogenicity response, collection and storage of serum samples (for potential analysis) is recommended if needed for interpretation of the study. Consistent with the existing biosimilar nonclinical/clinical guideline, the biosimilar mAb guideline states that other toxicology studies (e.g. safety pharmacology, reproductive toxicology) are not required. The biosimilar mAb guideline also recommends that a stepwise approach be applied to the clinical studies, with PK studies being Step 1, and clinical efficacy being Step 2.

Like generic medicines, biosimilars are intended to be administered using the same dose(s) and dosing regimen to treat the same disease(s) as their reference product [1]. Thus, while the guideline iterates that comparative clinical studies should always be conducted, it does emphasize that the focus of the biosimilarity exercise is to "demonstrate similar efficacy and safety compared to the reference product, not patient benefit per se, which has already been established by the reference product." As such, the design, patient population, and efficacy/safety endpoints used in the comparative clinical study(ies) may be different from those used previously to establish the therapeutic benefit of the reference product [1]. The population selected for the comparative PK studies should be homogeneous and sufficiently sensitive, and while healthy volunteers often have less variability in PK (compared to patients), it may not be possible to conduct the comparative PK study in this population (e.g. the adverse events profile of the reference product renders the risk too high to conduct the study in healthy volunteers) [32].

The comparative PK studies can be combined with PD endpoints (if available), which may contribute valuable information to the comparability exercise. If relevant PD markers of clinical efficacy are available, applicants should explore the potential to evaluate dose–concentration–response relationships (or time–response relationships). This approach may provide pivotal evidence of similarity in some cases, provided that a clear dose–response relationship is shown and that at least one PD endpoint is an accepted surrogate marker of clinical efficacy and can be related to patient outcome. If a comparative PK/PD study cannot convincingly demonstrate comparability in a clinically relevant manner, comparative efficacy will be a necessary part of the clinical approach. Several important concepts regarding clinical efficacy and safety should be considered when developing the clinical comparability exercise. In general, the most sensitive patient population and clinical endpoint (measure of efficacy) is recommended to determine product-related differences (between the proposed biosimilar and reference product), and to reduce patient and disease-related factors to increase the accuracy of data interpretation. If available, appropriate PD endpoints should be measured in addition to the preferred clinical endpoints of efficacy. Importantly, the guideline notes that while the preferred endpoint to show efficacy in cancer indications for a novel anticancer mAb would be either progression-free/disease-free survival or overall survival, these endpoints may not be feasible or sufficiently sensitive to demonstrate similar efficacy between a biosimilar mAb and a reference product. Thus, in the anticancer setting, a clinical trial in a homogeneous patient population evaluating a clinical endpoint that measures activity, such as overall response rate, may be considered as the primary endpoint [32].

Safety is key throughout the clinical development, and the guideline emphasizes that the safety of patients cannot be compromised by a comparability exercise. The type, severity, and frequency of adverse reactions between the proposed biosimilar and reference product should be compared, particularly the adverse events described for the reference product. Another concept regarding clinical comparability is immunogenicity, which should be assessed before approval. The biosimilar mAb guideline states that, due to the clinical consequences associated with immunogenicity (e.g. toxicity or loss of efficacy), comparative evaluation of the immunogenicity profile between the proposed biosimilar mAb and the reference product is important. Long-term immunogenicity and safety data may be required post authorization, which the applicant would describe in the proposed risk management/pharmacovigilance plan as part of the marketing authorization process. While the guideline states that extrapolation of indications is possible with evidence of similarity, if the mechanism of action of the mAb differs for

the claimed indications (e.g. reference product licensed as an anticancer agent and immunomodulator), relevant data to support extrapolation to all claimed indications are necessary.

Since the approval of Omnitrope® in 2006 (the first biosimilar approved in Europe), the EMA has gained substantial experience which has led the EMA to revisit and revise many of the existing guidelines. The general guidelines, for example, are currently being revised (www.ema.europa.eu). The concept papers for the revision of the "overarching" and nonclinical/clinical guidelines were adopted by the Committee for Medicinal Products for Human Use (CHMP) for release for consultation in November 2011 (EMA/CHMP/BMWP/572643/2011) and September 2011 (EMA/CHMP/BMWP/572828/2011), respectively, and the draft guideline for the revision of the quality guideline was released for consultation in May 2012 (EMA/CHMP/BWP/247713/2012). In addition, many of the product class-specific guidelines have been revised, such as the guideline on biosimilar recombinant erythropoietins (the revised guideline [EMEA/CHMP/BMWP/301636/2008] became effective October 2010) or are under revision, such as the concept paper for the revision of the guideline on biosimilar low molecular heparins which was released for consultation on July 2011 (EMA/CHMP/BMWP/522386/2011). As described above, the existing EU guidelines (EMEA/CHMP/437/704 and EMEA/CHMP/BMWP/49348/2005) [26,28] state that the reference product used in the comparability exercise must be authorized in the EC on the basis of a complete dossier, and that while some data from comparability studies conducted with an ex-EU-licensed reference product may be acceptable, they can be used only for supportive purposes. However, in September 2012, the EMA updated the Questions and Answers document specific to biosimilars (EMA/837805/2011), stating that the EC intends to accept data from certain nonclinical and clinical studies using ex-EU-licensed reference products for the demonstration of similarity (see Question 4 of the Question and Answers document EMA/940451/2011; available at www.ema.europa.eu/ema).

Since the implementation of the regulatory pathway for the approval of biosimilars, numerous applications for biosimilar products have been received by the EMA (EMA Applications for New Medicine, April 2012 [1,33]). In April 2012, the EMA received the first application for a biosimilar mAb infliximab, and as of September 2012, seven biosimilar applications have been submitted to the EMA and are under review: two for biosimilar infliximab, three for biosimilar human insulin, one for biosimilar follitropin alfa, and one for biosimilar filgrastim (EMA/584368/2012 corr; available at www.ema.europa.eu) [31]. The EU has led the way in establishing a formal regulatory pathway for the approval of biosimilars, and has taken a transparent, science-driven, and evidence-based approach in the process of establishing the regulatory guidelines for biosimilars. The EMA biosimilar guidelines issued to date have been viewed as appropriate and successful in ensuring product efficacy and safety. As such, many of the scientific principles and standards of the EMA guidelines have been adopted by other regions [21].

## THE WORLD HEALTH ORGANIZATION GUIDANCE ON BIOSIMILARS

Many biosimilar manufacturers are seeking approval in countries where the National Regulatory Authority (NRA) is yet to establish a formal regulatory pathway in their region.

Recognizing the need for guidance in regions where guidance is not yet established, the WHO—the public health arm of the United Nations—developed a guideline to provide globally acceptable scientific principles and standards for the quality, nonclinical, and clinical data required for the approval of biosimilar products [20,21]. The scientific basis for developing a WHO guideline on biosimilars was discussed and agreed upon at the first WHO Informal Consultation on Regulatory Evaluation of Therapeutic Biological Medicinal Products in 2007. Subsequently, the WHO issued the guideline through its Expert Committee on Biological Standardization (ECBS), which was adopted at the 60th meeting of the WHO ECBS in October 2009 [30]. The guideline was developed and written by members of several regulatory authorities in countries around the world, such as the United States, Europe, Japan, Canada, Korea, and India, as well as interested stakeholders including trade associations (e.g. European Generic Medicines Agency) and industry [20].

Overall, the standards of the WHO guideline were derived largely from the biosimilar guidelines established in highly regulated regions (e.g. EU, Australia, Canada, and Japan), and they provide "globally accepted norms and standards for the development of biosimilar products" [20]. The scope of the WHO guideline includes recombinant DNA-derived therapeutic proteins, and the guideline notes that biologics such as vaccines, plasma-derived products, and their recombinant analogs are excluded, referring the reader to other regulatory guidance for such products (www.who.int/biological/areas/en/). Similar to the principles of the EU biosimilar guidelines, the WHO guideline states a stepwise approach be used in the development of a proposed biosimilar product, starting with comparative analytical characterization studies, followed by comparative nonclinical and then clinical studies. The sponsor must provide to the NRA the basis for selecting the reference product used in the comparability exercise. In some regions, the country where licensure for a biosimilar is sought may lack an approved reference product. In such cases, the WHO guideline suggests that a reference product may be acceptable, if it is licensed on full quality, safety, and efficacy data that is widely marketed for a suitable duration in another jurisdiction with a well-established regulatory framework [20,21]. Consistent with the European guidelines, the same reference product should be used throughout the comparability exercise (quality, nonclinical, and clinical studies), and the drug substance, dosage form, and route of administration of the proposed biosimilar should be the same as the reference product. In terms of the quality data, comprehensive and comparative (i.e. head to head with the reference product in the same study) physiochemical and biological characterization of the proposed biosimilar is required. The analytical demonstration of similarity between the proposed biosimilar and reference product is the basis for the potential reduction of the nonclinical and clinical data. While some differences in quality attributes will likely be detected, the sponsor will need to evaluate the potential impact of such differences on clinical efficacy and safety.

Many of the expectations of the WHO guideline for the nonclinical data required for the approval of a biosimilar are similar to other regional guidelines, including the EMA biosimilar guidelines. The nonclinical studies should be conducted with the final formulation of the proposed biosimilar (unless otherwise justified), should include comparative *in vitro* (e.g. receptor-binding studies, cell proliferation, or cytotoxicity assays) and *in vivo* (e.g. pharmacologically relevant animal model) studies, and at least one repeat-dose comparative toxicity study (including TK and ADA responses) should be conducted.

The WHO guideline describes various scientific concepts that should be considered in the clinical comparability exercise as well as points to consider in the design of the clinical studies. The clinical comparability exercise is a stepwise procedure that should begin with comparative PK (or PK/PD if feasible) studies, followed by the pivotal clinical efficacy and safety studies. The study design (e.g. single vs. repeated-dose; crossover vs. parallel) and population (e.g. healthy volunteers vs. patients) for the PK studies should be scientifically justified, and the acceptance criteria for the demonstration of similar PK between the biosimilar and reference product should be pre-specified. In general, comparative clinical efficacy studies are required, although in some cases, comparative PK/PD studies may be sufficient provided that certain conditions are met such as adequate characterization of the reference product's PK and PD properties. The comparative efficacy studies should be controlled, sufficiently powered, and double blind (or, at a minimum, observer blind). Equivalence trials are preferable (vs. non-inferiority designs) to ensure that the proposed biosimilar is not clinically less or more potent than the reference product when used at the same dosage(s). In addition, an advantage of an equivalence design (over a non-inferiority design) is that it provides a strong rationale for the potential of extrapolation of efficacy to other indications of the reference product. Prior to approval, the safety of the proposed biosimilar must be evaluated in a sufficient number of patients, and the type, frequency, and severity of adverse events between the biosimilar and reference product should be compared. In addition to safety, the frequency, type, and clinical consequence of the immunogenicity response should be compared between the biosimilar and reference product. The WHO guideline notes that the clinical studies are often too small and limited to fully identify the safety concerns and immunogenicity profile of a biosimilar product, and therefore, further characterization of the safety and immunogenicity profile of the biosimilar may be necessary in all approved indications post approval. At the time of the marketing authorization, the applicant must have an established risk management and pharmacovigilance (PV) plan where any specific safety monitoring imposed on the reference product (or product class) should be included in the PV plan. The WHO guidelines also specify the roles and responsibilities of an NRA, including that the NRA provide a legal framework for proper PV surveillance and ensure specific identification (i.e. traceability) of any biologic marketed in their territory that may be the subject of adverse event reports.

## REGULATORY PATHWAY FOR BIOSIMILAR PRODUCTS IN THE UNITED STATES

### Overview

In the United States, chemical (small-molecule) pharmaceuticals are regulated and licensed for marketing under the Food Drug and Cosmetic Act (FDCA), whereas, biologic products are regulated and approved under the Public Health Services Act (PHSA) [34,35]. While biologic products are registered through the PHSA, a historical "glitch" has caused certain natural source biologic products, such as insulin and human growth hormone, to be regulated as chemical drugs under the FDCA [34,35].

The approval of generic products through an abbreviated new drug application (ANDA) pathway under the Drug Price Competition and Patent Term Restoration Act

("Hatch-Waxman") requires that the active ingredient in the proposed generic medicine and the reference product be identical. Having the active ingredient of the proposed generic be identical to the reference product allows the generic manufacturer to rely on, or "reference," the FDA's previous finding of efficacy and safety of the approved reference product [34]. Thus, the demonstration of therapeutic equivalence and interchangeability in clinical studies is not required for generic products under an ANDA application [8,9]. As described previously, due to the complexity of biologic products and their manufacturing processes, the active substance of a proposed biosimilar is similar (but not identical) to the reference product, and differences in product attributes (e.g. posttranslational modifications or the three-dimensional shape) can influence the biologic's functional activity [5,7,34]. Thus, the approval process under Hatch-Waxman is not applicable for proposed biosimilar products [34,36–38].

On March 23, 2010, President Obama signed into law the Patient Protection and Affordable Health Care Act or PPACA (Pub. L. No. 111-148), which included the Biologics Price Competition and Innovation Act of 2009 (BPCIA). The BPCIA amended the PHSA, adding sections that authorize the Secretary of the US Department of Health and Human Services ("the Secretary") to approve a proposed biosimilar product under an abbreviated pathway called 351(k) if the proposed biosimilar is demonstrated to be highly similar to a biologic product (reference product) already approved as a Biologics License Application (Section 351 (a)) under the PHSA [3,22,39]. An abbreviated approval pathway for copies of small-molecule pharmaceuticals has been established since the Hatch-Waxman Act was enacted in 1984.

The BPCIA differs from Hatch-Waxman, requiring that certain standards be met for the approval of biologic products as "biosimilar" or "interchangeable [40]." The BPCIA defines biosimilarity as the proposed biosimilar being "highly similar to the reference product notwithstanding minor differences in clinically inactive components," and if there are "no clinically meaningful differences" between the proposed biological product and the reference product in terms of "safety, purity and potency [3,21,22,39]." Under the BPCIA, the demonstration of biosimilarity requires biosimilar applicants to provide data from three categories of study:

- analytical studies demonstrating that the proposed biosimilar is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
- animal studies (including an assessment of toxicity); and
- a clinical study or studies (including an assessment of immunogenicity, and pharmacokinetics or pharmacodynamics) sufficient to demonstrate safety, purity, and potency of the proposed biosimilar.

In addition, under the 351(k) pathway, a biosimilar applicant may seek a determination of interchangeability from the FDA in the initial application or a later supplement. According to the BPCIA, biosimilar products deemed interchangeable by the FDA may be substituted for the reference product by a pharmacist without the intervention of the prescribing healthcare provider [39]. When a biologic protein product is deemed highly similar to the reference product (biosimilarity determination), it cannot be assumed that the biosimilar is interchangeable with the reference product. The BPCIA distinguishes the approval standards between a determination of biosimilarity and a determination of interchangeability, with the more stringent standards required for an interchangeability designation. The

BPCIA authorizes an interchangeability designation by the FDA when certain conditions have been met:

- The proposed product is biosimilar to the reference product.
- The proposed biosimilar can be expected to produce the same clinical result as the reference product in any given patient.
- The safety and diminished efficacy of switching a patient between the proposed biosimilar and reference product is not greater than repeat use of the reference product without switching [3,21,30,39].

It is important to note that while the BPCIA defines the standards for demonstrating biosimilarity to an innovator biologic product, the US Congress authorized the FDA to define the scientific standards and extent of data necessary to demonstrate that a proposed biosimilar is highly similar to a reference product; therefore the Secretary has the discretion to determine that an element of the data (considered for a showing of biosimilarity) is unnecessary, and to waive any of these application requirements [3,21,22].

In their effort to implement the BPCIA, the FDA established a working group to address the agency's approach to approving biosimilar products and ensure that the review and approval process for 351(k) applications is consistent and conducted in an efficient and scientifically sound manner (Implementation of the BPCIA of 2009 [39]). The FDA established a Biosimilars Implementation Committee (BIC), which is co-chaired by Dr. Janet Woodcock (Director of the Center for Drug Evaluation Research [CDER]) and Dr. Karen Midthun (Director of the Center for Biologics Evaluation Research [CBER]) [39]. The role of the BIC, which consists of CDER and CBER staff and members from the Office of Chief Counsel and the Office of the Commissioner, is to evaluate the law and work on the necessary steps towards implementing the approval process for biosimilars, as well as policy development and budget and resource planning [39]. In addition, two Biosimilar Review Committees (BRC) were chartered, which consist of members from both CDER (CDER BRC) and CBER (CBER BRC). The CDER/CBER BRC is responsible for addressing product-specific issues associated with scientific methodology, considering requests of applicants for advice regarding their proposed development program for a biosimilar product, and reviewing 351(k) applications [39].

Following the enactment of the BPCIA, the BIC held a two-day public hearing (November 2–3, 2010) to obtain input from interested stakeholders on specific issues and challenges relating to implementation of the BPCIA; interested parties attending the meeting included representatives of the pharmaceutical/biopharmaceutical industry (innovator and generic manufacturers), patient advocacy groups, healthcare institutions, and pharmaceutical/biopharmaceutical trade associations. Questions asked by the agency covered a range of critical topics, such as biosimilarity, interchangeability, exclusivity, patient safety and PV, definition of a biological product, and user fees [41].

On February 9, 2012, the FDA issued three draft guidance documents covering the development and approval of biosimilar products [42].

- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (referred to as the Quality guideline in this chapter) (Docket No. FDA-2011-D-0602)
- Scientific Considerations in Demonstrating Biosimilarity to a Reference Protein Product (referred to as the Scientific guideline in this chapter) (Docket No. FDA-2011-D-0605)

- Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (referred to as the Q&A guideline in this chapter) (Docket No. FDA-2011-D-0611).

The FDA held a one-day public hearing on May 11, 2012, to hear testimony and obtain input from key stakeholders (e.g. pharmaceutical/biopharmaceutical industry, patient advocacy groups, healthcare providers, etc.) on critical topics on the draft guidance documents [43]. Another draft biosimilar guidance titled Submission of Clinical Pharmacology Data as Evidence of Biosimilarity for Biologics and Protein Products is expected to be released by the FDA in 2013 [44]. In addition, the FDA has indicated that guidance on interchangeability will be issued in the future, but it is not known when such guidance will be available.

These three draft guidance documents, which cite one another throughout each document, provide general guidelines for manufacturers seeking to file a 351(k) application for the licensure of a biologic product. While the 351(k) pathway applies generally to biological products, the draft guidance documents focus on therapeutic protein products and provide an overview on the scientific and analytical considerations in demonstrating biosimilarity between a proposed protein product and a reference product (see Scientific guidance). The Scientific and Quality guidance documents address the quality, nonclinical, and clinical information necessary to establish biosimilarity between a proposed biosimilar and reference product, and the Q&A guidance provides the agency's answers to questions commonly asked by biosimilar sponsors and other interested parties regarding FDA's interpretation of the BPCIA.

General recommendations and considerations are described throughout all three guidance documents. For example, the agency strongly encourages biosimilar sponsors to meet with the FDA early in their development program, to provide an overview of the proposed development program and discuss various issues, such as those relating to the chemistry, manufacturing, and controls (CMC), and to discuss the sponsor's proposed approach to demonstrating biosimilarity, and establish a schedule for product development milestones to serve as landmarks for future meetings with the agency (see Q&A guidance). Rather than applying a "one-size-fits-all" approach, the FDA reiterates repeatedly in the draft guidance that it intends to apply a "totality-of-evidence" approach to evaluate all available data and information submitted when reviewing 351(k) applications. In addition, the agency will assess the amount and type of data necessary to support a demonstration of biosimilarity on a case-by-case basis (see Scientific guidance). Importantly, the draft guidance recommends that sponsors apply a "stepwise approach" to develop the data (analytical, nonclinical, and clinical) to demonstrate biosimilarity, and at each step, the sponsor should assess the extent of residual uncertainty that remains regarding the similarity of the proposed biosimilar product and the reference product (see Scientific guidance). The draft guidance emphasizes that the stepwise approach to demonstrating similarity should begin with extensive comparative structural (e.g. amino acid sequence, protein folding and higher order structures, post-translational modifications) and functional (e.g. target binding, enzyme kinetics or cell-based pharmacological/biological activity assays) characterization of the proposed biosimilar and the reference product, and that a robust comparative physiochemical and functional characterization is the foundation of the biosimilar development program in providing evidence of similarity or differences between the proposed biosimilar and the reference product (Scientific and Quality guidance).

## Quality Guidance

The draft Quality guideline focuses on the CMC topics, and reviews the analytical studies that may be relevant to evaluating the similarity between the proposed biosimilar and the reference product. As described above, because a robust, comparative physiochemical and functional characterization serves as the foundation in the biosimilar program, the agency expects manufacturers to use state-of-the-art technology in the analytical studies. In addition, the Quality guidance (and Scientific guidance) describes applying a "fingerprint-like" analysis algorithm to further quantify the similarities or differences in product attributes between the proposed biosimilar and the reference product using a combination of highly sensitive, orthogonal methods. Accordingly, the guidance describes how this strategy of rigorous physiochemical and functional comparisons increases the potential to detect minimal or no differences between the proposed biosimilar and the reference product, and thus provides stronger scientific justification for the sponsor to use a more "selective and targeted" (abbreviated) approach for the nonclinical (animal) and/or clinical studies to support a demonstration of biosimilarity. The Quality guidance also recommends other factors that sponsors should consider when assessing biosimilarity, such as:

- an appropriate number of lots of the proposed biosimilar and reference product should be evaluated in the comparative analytical tests;
- product- and process-related impurities of the proposed biosimilar should be identified, characterized, and quantified and compared to those of the reference product (to the extent feasible and relevant);
- comparative stability tests (including accelerated stability) are performed.

## Scientific Guidance

The draft Scientific guidance provides a general review of the comparative structural and functional characterization necessary for demonstrating biosimilarity, but it primarily addresses the nonclinical and clinical data necessary for establishing biosimilarity. As stated above, the BPCIA gives the FDA the authority to determine whether an element (including nonclinical and clinical data) is unnecessary for the demonstration of biosimilarity, which allows the agency to eliminate animal and/or clinical studies that are redundant (and potentially unethical) and not necessary for the biosimilarity determination [3,21,39]. The guidance explains that the type and extent of nonclinical and clinical data required for the demonstration of biosimilarity will depend on the amount of "residual uncertainty" that remains based on the results of the comparative physiochemical and functional characterization (see Scientific guidance).

Regarding animal toxicity studies, the draft guidance states that animal toxicity data are considered useful when uncertainties about the safety of the proposed biosimilar product remain based on the results of the physiochemical and functional characterization, and the scope and extent of animal toxicity studies depends on what is known about the reference product and the proposed biosimilar. In addition, while the guidance asserts that animal toxicity studies are generally not useful when a pharmacologically relevant animal species is not available, in some instances, data (e.g. PK and/or systemic tolerability) from

a nonrelevant animal species may be useful to support clinical trials with "a proposed product that has not been previously tested in human subjects." When a sponsor considers animal toxicity studies are not warranted in the biosimilarity exercise, the sponsor must provide scientific justification based on data from comparative analytical and functional bioassays/*in vitro* studies. When animal toxicity studies are conducted, the guidance asserts that they should be comparative, and various factors, such as dose selection, study duration, and animal species must be considered. Rather than requiring a comparative standard toxicity (terminal) study using the proposed biosimilar and reference product, other study designs may be considered, such as a stand-alone toxicity study using only the proposed biosimilar product, or a comparative single-dose PK/PD (non-terminal) study. The design of the animal toxicity study should be consistent with the principles of ICH S6(R1), and must be scientifically justified. The Scientific guidance asserts that assessment of animal immunogenicity is generally not predictive of human immunogenic responses; however, the guidance does state that since differences between the proposed biosimilar and reference product in certain product attributes and/or impurities/excipients may affect ADA responses, and therefore, measurement of ADA responses in animal studies may provide useful information relevant to patient safety. Other toxicology studies conducted for approval of an innovator biologic product (e.g. safety pharmacology, reproductive and developmental toxicity, carcinogenicity studies) are not generally necessary when biosimilarity has been demonstrated through the physiochemical/functional characterization and animal toxicity studies; however, certain specific clinical safety concerns regarding the reference product may warrant additional animal studies with the proposed biosimilar product.

## Q&A Guidance

The objective of the Q&A guidance document is to promote transparency for the development of biosimilar products and provide the FDA's responses to questions commonly raised by biosimilar applicants and other interested parties regarding the agency's interpretation of the BPCIA. The Q&A guidance addresses several key topics regarding the development and approval of biosimilar products, including (1) definition of protein, (2) reliance of comparative data from non-US-licensed products, and (3) interchangeability.

The BPCIA amends the definition of "biological product" to include a "protein (except any chemically synthesized polypeptide)"; thus, an application for a biologic product must be submitted under the PHSA (as opposed to the FDCA for non-biologic [small-molecule] products). In the draft guidance, the FDA provides further definition regarding the category of "protein" to identify the statutory authority under which therapeutic products will be regulated (i.e. FDCA or PHSA), and defines a "protein" as any alpha amino acid polymer with a specific defined sequence greater than 40 amino acids in size. In contrast, the agency defines a "chemically synthesized polypeptide" as an alpha amino acid polymer made by chemical synthesis and less than 100 amino acids in size. Thus, the guidance clarifies that a "protein" will be regulated as a biologic product under the PHSA, whereas a "chemically synthesized polypeptide," which is not a biologic product, will be regulated under the FDCA (unless it otherwise meets the statutory definition of a biologic product) (see Q&A guidance).

The draft guidance also addresses allowing biosimilar sponsors to use certain data obtained from studies using a non-US-licensed reference product in support of the demonstration of biosimilarity. Based on the BPCIA, a proposed biosimilar product must be evaluated against a reference product licensed under section 351(a) of the PHSA [3,21,39]. The statute prohibits reliance on the use of nonclinical or clinical data generated in studies using non-US-licensed reference products. Therefore, based on the law, manufacturers that have a biosimilar product already licensed in another country (which used a non-US-licensed reference product for the demonstration of biosimilarity) seeking approval in the US would be required to perform comparative nonclinical and/or clinical studies with the US-licensed reference product. This statutory constraint raised major concerns for biosimilar manufacturers seeking approval in the US because some sponsors would be required to repeat full nonclinical and/or clinical studies with the US-licensed product, which in many cases, could be viewed as an unethical and unnecessary duplication of animal and human testing. To avoid the unnecessary duplication of animal and clinical studies, the FDA will consider the use of a non-US-licensed comparator product in certain studies (nonclinical and/or clinical), to support a demonstration that the proposed biosimilar product is biosimilar to the US-licensed reference product. If a biosimilar applicant uses data from a non-US-licensed product, the sponsor should provide adequate information to scientifically justify the relevance of the comparative data as well as establish an acceptable bridge to the US-licensed reference product. In addition, the guidance states that the bridge between the non-US-licensed and US-licensed reference product will include a three-way analytical comparison of the proposed biosimilar, non-US-licensed product and the US-licensed reference product, and at least one clinical PK study (and PD study, if appropriate) to support the demonstration of biosimilarity of the proposed biosimilar directly to the US-licensed reference product. Sponsors should consider various factors when using data generated from studies using non-US-licensed product in the biosimilarity development program, such as the relationship between the license holder of the non-US-licensed product and the license holder for the US-licensed reference product (e.g. the non-US-licensed product or components thereof are manufactured in the same facility as the US-licensed reference product) and whether the non-US-licensed reference product was manufactured under a regulatory agency with standards similar to the FDA.

As described above, biosimilar products also may be determined to be interchangeable with the reference product under the BPCIA [3,12,39]. While the Q&A guidance discusses interchangeability, it does not directly address the requirements for determining if a proposed biosimilar is interchangeable with a reference product. According to the FDA, the determination of biosimilarity and interchangeability are sequential, and given the statutory standards for an interchangeability determination, it would be difficult to determine whether a proposed biosimilar product is interchangeable with a reference product in an original 351(k) application. The agency, however, states that it will continue to identify the information necessary to make a determination of interchangeability. In addition, the FDA will develop standards to ensure that biologic products that are not deemed interchangeable are not inadvertently substituted for a reference product in the absence of the prescriber's consent [45].

## BIOSIMILAR PATHWAYS IN OTHER REGIONS

As described above, subsequent to the EMA issuing the overarching biosimilar guidelines in 2005/2006, countries around the world began to issue regulatory guidance documents for the approval of biosimilar products in their regions. Overall, under the biosimilar guidelines for the major regulated regions (e.g. US, EU, Canada, Japan), a demonstration of biosimilarity is made through a stepwise, comprehensive comparability exercise.

The process begins with a comparison of the analytical (physiochemical and biological/functional) properties, followed by nonclinical and clinical studies, and the type and extent of the nonclinical and/or clinical studies being based on the robustness and outcome of the comparative analytical studies.

### Australia

The regulatory body for therapeutic products (e.g. medicines, medical devices, blood and blood products) in Australia is the Therapeutic Goods Administration (TGA), which is a division of the Australian Government Department of Health and Ageing. Australia adopted the EMA general biosimilar guidelines (e.g. overarching; nonclinical/clinical issues; quality issues) in 2008. In addition, Australia adopted the EMA product-specific biosimilar guidelines and they are posted on the TGA website (www.tga.gov.au) (with the exception of the revised biosimilar guideline for recombinant erythropoietins [EMEA/CHMP/BMWP/301636/08]).

### Canada

The federal regulatory authority that oversees the approval of medicinal products in Canada is the Therapeutic Products Directorate of Health Canada. Health Canada released guidance for biosimilar products in March 2010 (available online at http://www.hc-sc.gc.ca). While Canada's perspective and scientific standards for the demonstration of biosimilarity are comparable to the EMA general guidelines, the Canadian guidance does differ from the initial EMA guidelines in certain requirements for the reference product. As described above, the existing EU guidelines state that the reference product used in the comparability exercise must be authorized in the EC on the basis of a complete dossier (recall, however, that the EMA updated the biosimilars Questions and Answers document in September 2012, stating that the EC intends to accept the use of an ex-EU-licensed reference product; see above). However, the Canadian guidance does accept the use of a non-Canadian-licensed product, but the sponsor must show that the non-Canadian-licensed product is a "suitable proxy" for the version of the Canadian-licensed reference product (Canadian Biosimilar Guideline, 2010). The suitability of a biological product to serve as a reference product for a biosimilar in Canada depends on the following factors:

- Whether the original marketing authorization was based on a complete data package and has significant safety and efficacy data accumulated such that the demonstration of similarity will bring into relevance a substantial body of reliable data.
- When a non-Canadian reference product is used in the biosimilarity exercise, the applicant must demonstrate that the non-Canadian product is a suitable proxy for the version of the product approved in Canada.

- The non-Canadian biological product must be approved in a jurisdiction with an established relationship with Health Canada and be widely marketed in a jurisdiction that formally adopts the International Conference on Harmonisation guidelines and has regulatory standards, post-market surveillance activities, and approaches to comparability similar to those in Canada.
- The Canadian and non-Canadian products must be marketed by the same company and in the same dosage form.

Regarding the nonclinical studies, the Canadian Biosimilar Guideline states that the appropriate nonclinical studies should be conducted prior to the initiation of clinical trials, and these studies should be comparative in nature. In addition, consistent with the initial EMA biosimilar guideline (nonclinical/clinical issues), at least one repeat-dose toxicity study (including TK and ADA? parameters) should be conducted in a relevant animal species of sufficient duration so that potential differences in toxicity and/or immunogenicity responses can be detected.

## Japan

The regulatory body in Japan responsible for the scientific evaluation of medicines is the Ministry for Health Labour and Welfare (MHLW), and makes the decision on approval of pharmaceuticals, including biological products, for use in Japan. The Pharmaceuticals and Medical Devices Agency (PMDA) is a Japanese regulatory agency, which works with the MHLW, and conducts scientific reviews of applications for marketing authorization for pharmaceuticals, including biological products. The Office of Biologicals within PMDA provides consultations concerning the clinical trials of new medicines, including biosimilars.

The MHLW issued the biosimilar guideline in 2009, and overall, the scientific principles and approaches in the Japanese guideline are consistent with the existing EMA general biosimilar guidelines. In terms of the reference product, however, the Japanese guideline currently shows no flexibility in terms of accepting the use of foreign reference products, and asserts the reference product must be approved and licensed in Japan, as well as that the same reference product should be used throughout the comparability program. The Japanese guideline is limited in terms of addressing the nonclinical toxicity studies that are required as part of the biosimilarity exercise, stating only that repeat-dose toxicity studies in an appropriate animal species may be beneficial.

## Brazil

Many pharmaceutical and biopharmaceutical companies are interested in submitting licensing applications for marketing a proposed biosimilar product in countries with rapidly growing economies (“emerging markets”), such as Brazil and India; both of these countries have recently issued finalized regulatory guidance documents for the approval of biosimilar products.

In Brazil, the National Health Surveillance Agency (ANVISA), which is the Brazilian regulatory authority, was created in 1999 to protect the health of the citizens by means of the sanitary control of production and marketing of services and products, including

medicines, subject to sanitary surveillance (www.brasil.gov.br/sobre/health/organs/anvisa/br_mode11?set_language=en). Medicinal products are approved in Brazil once ANVISA has evaluated the evidence of the quality, efficacy, and safety of the medicine as presented by the applicant (http://portal.anvisa.gov.br/wps/portal/anvisa/home) [46]. Until 2002, no regulations specific to biological products existed in Brazil. The first regulation related to biological products issued in Brazil was RDC 80/2002; however, this regulation had the same pathway/data requirements for innovator and copies of biological products [47]. In an effort to encourage development of biological products (innovator and copies) in Brazil, it was recognized that the Brazilian regulations needed to be updated. ANVISA issued new regulations in 2010 (Resolution—RDC No. 55, December 2010) that define a specific regulatory pathway for innovator biological products and proposed biosimilars (ANVISA, No. 55, December 2010; RDC No. 55/2010 available online at http://portal.anvisa.gov.br/wps/portal/anvisa/home) [48]. The new Brazilian regulations are based on different regional regulations and guidelines, including the WHO guideline. While the Brazilian regulations follow many of the same scientific principles as the WHO guideline, there are some differences due to specific Brazilian laws and needs [47,49]. ANVISA requires that biosimilar products be at least as efficacious and safe as the innovator product and without contaminants. This burden of proof falls on the biosimilar applicant, and ANVISA decides on a case-by-case basis the extent of the clinical trial needed to demonstrate biosimilarity.

For biosimilar products, the ANVISA guidance outlines two approaches for submitting applications: a Comparative Development pathway and an Individual Development pathway [49]. The Comparative Development pathway outlines an approach in which the proposed biosimilar is compared directly to the innovator biological product in terms of the analytical studies. The nonclinical and/or clinical studies may be abbreviated, depending on several factors including the results of the comparative analytical studies [47,49]. An advantage of the Comparative Development pathway is that it allows for extrapolation of indications. In the Individual Development pathway, a reduced dossier can be presented; however, while the quality/analytical data must be a complete package, the studies do not have to be comparative (e.g. head-to-head with the innovator product) [47,49]. With the Individual Development pathway, the scope and extent of the nonclinical and/or clinical studies may be abbreviated, but at least one comparative (with the innovator product) Phase III study (equivalence or non-inferiority) is required [46,49]. A caveat with the Individual Development pathway, however, is that extrapolation across indications is not accepted [47,49]. Thus, in Brazil, only copies of biological products licensed under the Comparative Development pathway are considered to be biosimilars and receive approval for extrapolations across indications of the innovator product.

## India

India is an emerging market of great interest for pharmaceutical companies because of its high population and investment potential in technology. India is an important region for the development and approval of biologicals, both innovative and biosimilar products. Over the years, several copies of biological products have been marketed in India. However, there have been concerns regarding the quality of these products and whether the copies are

truly similar (in terms of quality, safety, and efficacy) to the innovator products, particularly due to the lack of comparative studies being performed as part of the licensing application (source: www.biosimilarnews.com/indian-biosimilars-guidelines; www.biospectrumasia.com/print_article/biospectrum/analysis/3021/biosimilars-guidelines-a-step-direction-india) [50,51]. As a result of this concern, in coordination with input from the industry and academia, India's Central Drugs Standard Control Organization (the national regulatory authority for approval of drugs in India) in collaboration with the Department of Biotechnology issued a final guideline for biosimilar products in 2012 titled Guidelines on Similar Biologics: Regulatory Requirements for Marketing Authorization in India [52]. India's definition of a biosimilar is a biological product that is claimed to be "similar" in terms of quality, safety, and efficacy to a reference product that has been granted a marketing authorization in India by a competent authority on the basis of a complete dossier and with a history of safe use in India. The Indian guidance addresses the regulatory pathway regarding the manufacturing process and quality aspects for biosimilar products in India, and it also reviews the pre-approval regulatory requirements for the comparative quality, nonclinical, and clinical studies as well as the post-market requirements. According to the guidance, the proposed biosimilar must be comparable to the innovator product in quality, safety, and efficacy, as demonstrated by comparative quality, nonclinical, and clinical studies. While approval is possible with abbreviated clinical trials, it is based on the data from the comparative analytical studies as well as the ability of the manufacturer to show consistency in the production process [53]. Overall, the scientific principles and approaches of the Indian guidance are similar to those of the EMA general and FDA draft biosimilar guidance documents. Like the existing EMA biosimilar guidelines (nonclinical and clinical issues; EMEA/CHMP/BMWP/42832/2005), the Indian guidance states that at least one repeat-dose toxicity study (including evaluation of immunogenicity) should be conducted in a relevant animal species, and the duration of the study should generally be at least four weeks (with a two-week recovery period). Interestingly, and in contrast to the EMA and FDA draft guidelines, if a relevant animal model is not available, then toxicity studies need to be conducted in *two* animal species (one rodent; one non-rodent).

A major difference between the Indian regulations and those of Europe and the United States is the lack of data exclusivity for innovator products. In Europe and the United States, proposed biosimilar products cannot be approved until 10 (Europe) or 12 (United States) years after the regulatory approval of the innovator product. India, however, does not have this type of regulatory data exclusivity, and thus the only restrictions that apply in terms of when a proposed biosimilar can be approved is patent exclusivity, which is an even less significant barrier (compared to other countries such as those in Europe and the United States) given the less well-developed patent regime for biological products in India [54]. In India, the reference product used in the biosimilarity exercise must be approved in India under a complete data package/full dossier. However, if the reference product is not authorized in India, it should be licensed and marketed for at least four years with significant clinical safety and efficacy data. Because the majority of innovative biological products have been generated primarily in Europe and the United States, many recently developed reference products will fall into this category, and thus, biosimilar applicants will either have to wait until the reference product is approved in India or wait four years after it has been approved in another country [54,55].

## SUMMARY

In the upcoming years, more innovator biological products will come off patent, and the market for biosimilars will continue to grow globally. Biosimilar products will continue to play a major role in healthcare systems around the world, and as regulatory authorities in different regions receive more applications for the licensing and marketing of biosimilars, new issues and challenges will continue to arise. The regulatory authorities around the world, in collaboration with the pharmaceutical industry/biosimilar manufacturers, will need to work together to effectively and harmoniously address these challenges. Although regulations for biosimilar products continue to be established in more countries to support the global market for biosimilars, the science and analytical technology for the characterization of highly complex biological products will continue to advance. Therefore, the policy and regulatory guidelines for the evaluation and approval of biosimilar products will need to be revised periodically to reflect the current state-of-the-art technology.

While the WHO guideline provides an important first step in the global harmonization of the development and approval of biosimilar products, there are still key differences in some of the regulatory requirements across regions. Therefore, it is critical that regulatory standards for biosimilar products remain transparent across regions, and ultimately, that the approval standards be harmonized globally in the future. In order to achieve global harmonization, the regulatory authorities will need to work in partnership to define the appropriate scientific and regulatory standards for the approval of biosimilars, to ensure that patients have access to high-quality products.

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