



Biosimilars: Rationale and current regulatory landscape



Ewa Olech, MD

Department of Internal Medicine, University of Nevada School of Medicine, 1707 W Charleston Boulevard, Suite 220, Las Vegas, NV 89102

ARTICLE INFO

Keywords:

Biosimilar
Biologic
Innovator
Reference product
Chronic inflammatory diseases
Nomenclature
Biosimilarity
Regulatory guidance
Regulatory pathways
Generics
Small-molecule drugs
Development

ABSTRACT

Objectives: To discuss current terminology and the regulatory standards and processes involved in the development of biosimilars.

Methods: An Internet-based literature search through April 2015 was performed for information related to biosimilars in chronic inflammatory disorders. Keywords were as follows: biosimilar, development, manufacturing, characterization, structural, functional, preclinical, clinical, immunogenicity, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and ankylosing spondylitis. The European Medicines Agency (EMA) and US Food and Drug Administration (FDA) websites were searched for guidelines and information related to biosimilars.

Results: Biosimilars are products that are highly similar to the reference product regarding quality, biological activity, safety, and efficacy. Biosimilars are biological products and not generic drugs and, thus, do not follow the same regulatory pathways as generic molecules. Rigorous early-stage structural, functional, and analytical testing, followed by nonclinical and clinical analyses comparing a biosimilar with its reference product, are required to demonstrate biosimilarity in regulatory markets worldwide.

Conclusions: The addition of biosimilars to the market has the potential to improve access to biologic therapies. Many regulatory agencies have enacted stringent pathways, which must be followed for a biosimilar to be labeled and approved as such; following the pathways will help protect and maintain the integrity, quality, and safety of the biosimilar product.

© 2016 Published by Elsevier Inc.

Introduction

Biopharmaceuticals, also known as biologicals or biologics, are large complex molecules produced in living organisms [1]. Most biopharmaceuticals are proteins, but they can also include other biological products such as vaccines, toxins, antitoxins, allergenic products, nucleic acids, or other tissue and cellular products [1,2]. In turn, protein biologicals include those purified from their natural sources, although they are most often manufactured using recombinant technology [1]. Biologicals cover a range of complexity, including peptides such as human insulin, small proteins such as erythropoietin, and large proteins such as monoclonal antibodies (mAbs) or receptor fusion proteins [3].

Since the introduction of the first biopharmaceutical, recombinant human insulin approved in 1982 for therapeutic use [4], the number of biologicals, including mAbs, approved for human use has greatly increased [5]. Biologicals have revolutionized the management of many diseases, including chronic inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis (PsO), inflammatory bowel disease (IBD), and more recently, juvenile idiopathic arthritis (JIA) [1,6–8]; however, because of their complexity, the development process for biologicals is very time-consuming and costly [9,10].

The expiration of data protection or patents for first-generation biopharmaceuticals, followed by patent expiration on the first approved mAbs [5], have opened the possibility of developing biosimilars, that is, biological products similar, but not identical, to the originator or reference products. Biosimilars may be approved through a rigorous, though abbreviated, pathway that relies upon the extensive knowledge and experience gained with the reference product [3]. The advent of biosimilars could be beneficial by broadening access to biologic therapy for patients with chronic inflammatory disorders and other conditions as recommended in practice guidelines [10].

Due to the various regulations and nomenclature used through time and across geographical areas, some confusion exists about

This supplement was funded by Pfizer Inc. Ewa Olech, MD, was a paid consultant to Pfizer Inc for the research and/or authorship of this supplement. Medical writing and editorial support to prepare this supplement was provided by Guidemark Health and funded by Pfizer Inc. Ewa Olech has the following additional conflicts of interest to disclose: *consultant:* AbbVie Inc., Amgen Inc., Celgene Corporation, Genentech Inc., Janssen Pharmaceuticals Inc., Regeneron Pharmaceuticals Inc., Sanofi-Aventis U.S. LLC, and UCB Inc.; *research grants:* AbbVie Inc., Amgen Inc., Genentech Inc., UCB Inc., and Vertex Pharmaceuticals Incorporated.

E-mail addresses: eolech@unr.edu, ewaolech@yahoo.com

what constitutes biosimilarity. This article aims to clarify the concept of biosimilarity and the surrounding terminology, as well as provide an overview of the regulations governing the licensing and approval of biosimilars. The second article in this supplement, “Development of Biosimilars,” describes in more detail the scientific principles underlying the development and manufacture of biosimilars.

The biosimilar opportunity

More than a decade ago, biologic therapies were introduced for the management of patients with a variety of chronic inflammatory diseases. Biologic disease-modifying antirheumatic drugs (bDMARDs) such as tumor necrosis factor (TNF) antagonists have proven to be effective in controlling RA symptoms, delaying joint damage, and improving outcomes in patients who do not respond to first-line therapy with conventional (or small-molecule) disease-modifying antirheumatic drugs (DMARDs) [11]. Furthermore, a number of clinical trials have supported the commonly accepted view that early intervention can help slow progression, leading to improved patient outcomes [12]. The same is true for other inflammatory diseases (PsO, PsA, AS, and IBD) [6,11]. In fact, early intervention and use of biologic therapy are recommended in many guidelines for the treatment of these conditions [11,13–15].

Biosimilars may help address unmet medical needs by increasing the accessibility of biopharmaceutical therapies. If access to biologics can be increased, it is reasonable to expect that it may result in more treatment and earlier initiations, as recommended in the guidelines, as well as greater continuity of treatment. With the intent of reducing healthcare expenditures while preserving the quality of patient care, many governments have (or are in the process of) enacting legislation to allow for the regulation and licensing of biosimilars [16]. Since the approval of the first biosimilar in Europe in April 2006, somatropin (Omnitrope) [17], other countries also have adopted rigorous regulatory standards for biosimilar development, and additional biosimilars have been approved globally [10].

Biosimilar nomenclature and terminology

Biosimilars

Through time, various terms have emerged or been used in the literature to refer to biosimilars, including, but not limited to, biocomparables, biogenerics (now obsolete), follow-on biologics, noninnovator proteins, similar biopharmaceuticals, similar biotherapeutic products (SBPs), and subsequent entry biologics (SEBs)

(Table 1). Inconsistent nomenclature has created confusion and has even fostered apprehension regarding biosimilars, especially since similar terms have received different definitions, and some of these terms have been sometimes applied to products that may not have followed stringent regulatory guidelines to be considered biosimilars, such as intended copies or noncomparable biotherapeutic products [18,19].

The EMA's Committee for Medicinal Products for Human Use (CHMP), which is responsible for the scientific assessment of human medicines and pioneered the development of a regulatory framework, defines a biosimilar as a version of an already authorized biological medicinal product (the reference product) with demonstrated similarity in physicochemical characteristics, efficacy, and safety, based upon a comprehensive biosimilarity exercise between the reference product and the biosimilar [19,20]. The FDA initially used the term “follow-on protein products” to refer to “proteins and peptides that are intended to be sufficiently similar to a product already approved under the Federal Food, Drug, and Cosmetic Act or licensed under the Public Health Service Act” [21]. Following the enactment of an approval pathway for such products [through the Biologics Price Competition and Innovation (BPCI) Act, part of the Patient Protection and Affordable Care (PPAC) Act, signed into law on March 23, 2010], the term was changed to biosimilars in the United States, as recommended by Weise et al. [19] in order to avoid confusion with the terminology [22].

Currently, the FDA defines a biosimilar as “a biological product that is highly similar to a US-licensed reference biological product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product for safety, purity, and potency of the product” [22]. Other regulatory agencies with rigorous regulatory processes in place have adopted their own terms for “biosimilars,” such as Health Canada’s “subsequent entry biologics” [23] or Mexico’s “biocomparables” [24], while the World Health Organization (WHO) refers to “similar biotherapeutic products” [5,25]. Although slightly different, these regulatory definitions and underlying regulations are based on consistent scientific principles [5]. It is important to note that the term “biogeneric” has now become obsolete and use of the term may lead to the erroneous interpretation that biosimilars are generics (see section *Biosimilars are not generics*) [1,19].

Second-generation biologics, biobetters, and intended copies

It is important to understand the difference between the concept of biosimilar and second-generation biologics, biobetters, and intended copies.

Table 1
Biosimilars nomenclature and definitions of biosimilars/biosimilarity according to different guidance documents

Country/region	Agency	Nomenclature	Definition
Canada	Health Canada	Subsequent Entry Biologics (SEBs)	A biologic drug that enters the market subsequent to a version previously authorized in Canada with demonstrated similarity to the reference biologic drug [23].
European Union	EMA	Biosimilar	Version of an already authorized biological medicinal product (the reference product) with demonstrated similarity in quality characteristics, biological activity, safety, and efficacy based on a comprehensive comparability exercise [20].
Mexico	COFEPRIS [24]	Biocomparables	Subsequent entry (after patent expiration) biopharmaceuticals that demonstrate comparable quality, safety, and efficacy profiles to those of the innovator reference product [24].
United States of America	FDA	Biosimilar (formerly, follow-on protein products) [21]	A biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components and demonstrates no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product [47].
Worldwide	WHO	Similar biotherapeutic products (SBPs)	Biotherapeutic product that is similar in quality, safety, and efficacy to an already licensed reference biotherapeutic product [26].

COFEPRIS, Comisión Federal para la Protección contra Riesgos Sanitarios; EMA, European Medicines Agency; FDA, US Food and Drug Administration; WHO, World Health Organization.

Second- (or next-) generation products are biologics that have been structurally altered to gain an improved or different clinical performance [1]—for example, a chimeric mAb and its fully human mAb counterpart, or a cytokine product and its PEGylated version. These improved next-generation versions of originator biologics are referred to as biobetters. Improvements may range from a longer half-life, allowing for less frequent dosing, to more potency with less adverse events (AEs) [26]. Molecules with the same mechanism of action but different structures, such as adalimumab or golimumab, developed subsequent to the first-generation biologic (infliximab), have also been termed second- or later-generation biologics [27]. None of these products are biosimilars since they differ in the structure of the active substance and/or exhibit different clinical behavior due to different potency or immunogenicity [19,21]. Given that biosimilarity, as defined by regulatory agencies such as the EMA and FDA, implies equivalent (neither better nor worse) efficacy and safety to that of the reference product [19,28], biobetters cannot qualify as biosimilars.

Intended copies, also known as “me-too biologics,” “noncomparable biologics” [29], “noninnovator biologics,” “noncomparable biotherapeutic products,” and other terms (e.g., “bio-alike” [30]) are noninnovator biopharmaceutical products that, unlike biosimilars, do not go through a rigorous biosimilarity exercise with the reference product [29]. As a result, they may lack sufficient evidence to demonstrate similarity and may, therefore, exhibit clinically significant differences from the reference product. These products, consequently, may not fulfill the requirements to be considered biosimilars and referring to them as such may cause confusion [19,29]. In various regions of the world, especially in emerging markets, particularly middle- and lower-income countries in Asia and Latin America [30], intended copies of biologics have been developed and marketed as “biosimilars” [31]. The potential shortcomings of some of these copy versions of original biologic products are illustrated by a recent report involving intended copies of etanercept and rituximab in Colombia and Mexico [32]. An AE was experienced by 198 (30.6%) of 647 patients; 42 (21.2%) of the patients who received the rituximab intended copy experienced an AE on the first day. Of the patients treated with Etanar or InfiTAM (intended copies of etanercept) experiencing at least one AE (12 patients reporting 14 AEs), 57.1% of the AEs reported were of grade 3 severity and 71.4% were neurologic AEs. The most frequently reported AEs were rash (21.7%), throat AEs (16.7%), pharyngeal AEs (14.6%), and pruritus (10.6%), but seven grade 4 AEs also occurred. Grade 4 AEs included infection, allergic reaction, and leukopenia. In addition, therapeutic failure was reported in 7.6% of the cases [32]. These examples demonstrate the need for an effective pharmacovigilance program.

Biosimilars are not generics

Even though small-molecule generics and biosimilars are only marketed after expiration of the reference product’s patent, biosimilars cannot be considered generics [2]. The active ingredient of a biosimilar has been demonstrated as similar to its originator, but due to their complex nature and production in living systems, it is

Monoclonal Antibody

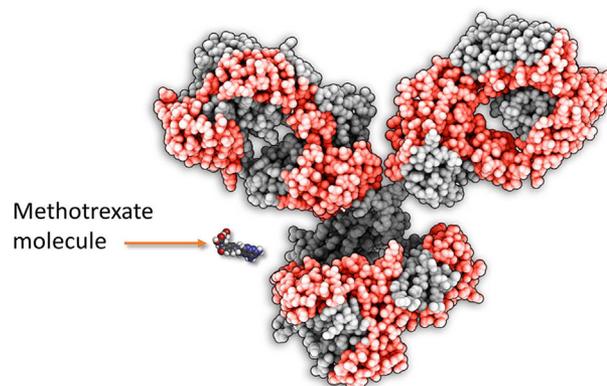


Fig. 1. Relative size of a monoclonal antibody compared with a small-molecule drug, methotrexate (454 Da); antibody (145,000 Da) [85,86].

not feasible to exactly duplicate the approved originator biologic [28]. Biosimilars, therefore, are not identical to the reference biologic and must undergo head-to-head comparisons with the originator at every step during development to ensure high similarity in physicochemical and functional characteristics, as well as safety and efficacy [28].

Differences between small-molecule drugs and biologics

Biologics, including biosimilars, differ substantively from small-molecule drugs in their molecular size, complexity, and manufacturing processes (Table 2) [33,34]. In contrast with small-molecule drugs, which typically have a molecular weight between 100 and 1000 Da, biologics have a chemical structure that is orders of magnitude larger and more complex, commonly ranging from approximately 18–150 kDa [35]. For example, the mAb shown in Figure 1 is approximately 300 times the size of methotrexate. In addition, as proteins, biologics are highly complex molecules with a primary structure (e.g., amino acid sequence), a secondary structure (e.g., folding), a tertiary structure that results from interactions between these secondary structures, and potentially a quaternary structure that results from the association of two or more individual protein subunits (e.g., hemoglobin) [2]. Small-molecule drugs, on the other hand, have much simpler molecular structures that are easily produced by chemical synthesis [2]. In contrast, biologics are typically produced by living cells, including bacteria, plant, and mammalian cells, via specialized manufacturing and purification processes [33,36,37]. As a consequence of structure and size, small-molecule drugs and biologics also differ in their route of administration. While chemically synthesized small-molecule drugs can generally be administered orally, biologics are most often delivered by parenteral administration [33].

Contrary to chemical synthesis, which generally results in 95% of chemically identical molecules, the living systems in which biosimilars are produced are inherently variable and result in heterogeneity due to variations in posttranslational modifications,

Table 2

Differences between biologics and small-molecule drugs

Characteristic	Small-molecule drug	Biological product
Manufacturing process	Chemically synthesized	Primarily produced in living cells
Size	Small: low molecular weight	Medium to large: high molecular weight
Complexity	Simple homogeneous structure	Complex, multiple levels of structure and posttranslational modifications (microheterogeneity)
Most common route of administration	Oral	Parenteral
Immunogenicity	Mostly nonimmunogenic	Immunogenic

such as glycosylation. In addition, they may undergo physical and chemical degradation, including deamidation, cleavage, and aggregation [33]. Therefore, biopharmaceuticals always consist of mixtures of variants of the same protein. It is important to note, however, that lots are tightly controlled and monitored to remain within predefined acceptable limits by manufacturers and regulatory agencies [33].

Furthermore, biologics, due in great part to their larger size, have the potential to be recognized by the body as “foreign,” and thus, have a greater ability to trigger an immune response (i.e., are more immunogenic) than small-molecule drugs, which are generally nonimmunogenic (too small to be recognized by the immune system) [33]. For biosimilars intended for chronic treatment, EU regulatory guidelines recommend a 12-month head-to-head comparative clinical study in which efficacy and safety, including immunogenicity, are compared between the biosimilar and reference product in the most sensitive population to detect potential differences [38,39].

The generic standard approval approach is not applicable to biosimilars

Generics, as chemically synthesized small-molecule drugs, share an identical molecular structure with their trade name product. For their licensing, in addition to demonstrating the same physicochemical characteristics, a generic drug must perform in the same manner in the body as its reference product. That is, the generic drug must be shown to be bioequivalent with the trade name product. Bioequivalence usually is established by demonstrating that the generic drug delivers the same concentration of active ingredient through the same time period as the trade name product [21,28]. Generic small-molecule drugs that are shown to be bioequivalent with the trade name product are recognized as therapeutically equivalent, therefore, demonstrating clinical efficacy and safety is not required for regulatory approval [33,40,41].

Developers of biosimilars do not have access to the originator companies’ proprietary data, including details on the manufacturing process, and, therefore, need to develop their own manufacturing process capable of producing a product as similar as possible to its reference product [5,42]. Although this is also the case for small-molecule generics, because the structure of the latter is more defined, manufacturing operations are more straightforward, and it is possible to generate an identical molecule [42]. This is more difficult with cell-based manufacturing processes, given biologics’ structural complexity, the product’s molecular heterogeneity, and differences in manufacturing as described above. Thus, a biosimilar cannot be identical with its reference product. The demonstration of bioequivalence in comparative bioavailability studies (which is the only requirement for chemically derived small molecules [34]) is insufficient to demonstrate therapeutic equivalence for biotechnology-derived products and additional clinical data in patients are required [28].

Differences between originator and biosimilar regulatory pathways

While the development process for both originator products and biosimilars involves analytical, nonclinical, and clinical testing, the development processes for a biosimilar and reference product emphasize different phases (Fig. 2). Originators must establish patient benefit *de novo* and, thus, require extensive clinical trials to demonstrate efficacy and safety [43]. For biosimilars, minimizing structural and functional differences with their reference product may allow reduced clinical testing requirements, relying on the clinical history of the reference biological product as much as possible, while decreasing any predictable impact on clinical safety and efficacy. In the United States, the requirements for the approval and license of complex biopharmaceuticals, including the targeted biological drugs used to treat inflammatory diseases, are specified in section 351(a) of the Public Health Service (PHS) Act. Biosimilars, on the other hand, are approved and licensed through a different section—section 351(k)—of the same Act [44]. Through the pathway established in section 351(k), biosimilar

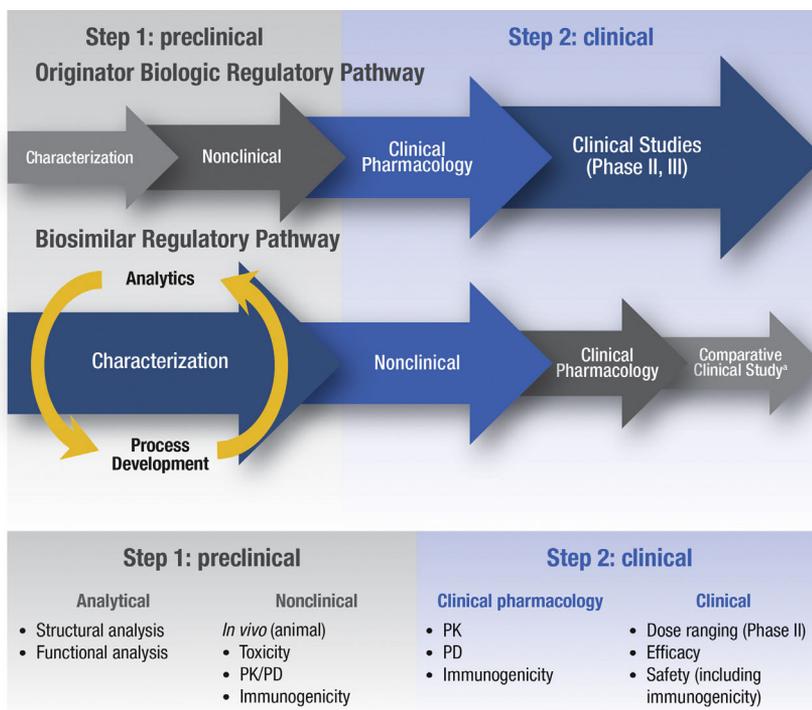


Fig. 2. Development pathways for originator biologic [section 351(a) of the Public Health Service Act] [87,88] and biosimilar [section 351(k) Public Health Service Act] [50].
^aConfirm safety and efficacy in a disease population (dose ranging not necessary).

licensing relies, in part, on the extensive knowledge gained with the originator (or reference) product, allowing for an abbreviated clinical data package [19,45]. As the reference product would have been licensed and marketed for many years [44], there should be a large body of knowledge on its efficacy and safety available [46]. Given that a biosimilar is intended to treat the same disease(s) as the reference product, with the same dose(s) and route(s) of administration, the focus of biosimilar development is, therefore, to demonstrate sufficient similarity and not to re-establish patient benefit [19,47]. EMA/FDA biosimilar guidelines recommend a stepwise approach to biosimilar development starting with comprehensive physicochemical and biological characterization. The extent and nature of further characterization in terms of comparative nonclinical and clinical testing depends on the level of evidence of similarity obtained in the previous steps. The quality data package is, therefore, the foundation of a biosimilar development program.

The reference product is the target in a biosimilar development program. The manufacturing process used by the originator for the reference product is proprietary information; therefore, a biosimilar manufacturer develops its own manufacturing process to reverse engineer the biosimilar to be as similar as possible to the reference product [48]. In order to obtain a highly similar molecule, multiple iterations of process conditions are evaluated with different clones prior to final selection [49]. This process forms the foundation of biosimilar development. Once similarity at the structural and functional level (highly similar molecule) is established, nonclinical and clinical development will serve to confirm similarity of safety and efficacy to the reference product [19,49]. Undergoing a complete clinical development package would defeat the purpose of biosimilar development and could even be considered unethical, as it would not provide additional information versus what is known for the reference product [19]. For example, for development of an originator biologic, phase II dose-finding studies must be conducted and safety and efficacy established within the determined dose range and route of administration. Consequently, nonclinical animal studies and phase I,

II, and large phase III clinical studies in humans are required. As biosimilars must be administered through the same route and at the same dose as the reference product [50], dose-finding studies are not required for biosimilar development, and generally, only pharmacokinetic (PK)/pharmacodynamic (PD) studies and a comparative clinical study in a sensitive population of patients to confirm efficacy equivalence between biosimilar and reference product are required [22]. With that said, although a reduction in the clinical and nonclinical data requirements is possible, the prelicensing data package is substantial (see second article of this supplement, "Development of Biosimilars," and previous articles in this supplement series) [19].

Demonstration of biosimilarity

To establish that the proposed biosimilar meets the requirements for biosimilarity, most regulatory agencies with strict requirements, including the EMA and FDA, require a rigorous, stepwise biosimilarity assessment, with each step building on previous steps [20,22]. An overview comparison of the EMA and FDA guidances presented in Table 3 highlights their similarities [51]. Under section 351(k) of the PHS Act, the FDA, in its evaluation of a biosimilar application, uses a risk-based, "totality-of-evidence" approach that considers both the quantity and quality of evidence. The proposed totality-of-evidence approach includes the evaluation of all data that support biosimilarity (quality characteristics, biological activity, safety, and efficacy) resulting from a comprehensive biosimilarity exercise to evaluate and license biosimilar products [22]. The EMA follows a similar approach for approval of biosimilar products [20].

Regulatory landscape

Despite the existence of the aforementioned slight differences in the definition and guidelines or requirements for evaluation and approval among different regions, the basic principles governing

Table 3
Comparing EMA and FDA guidance documents

Guidance	FDA position [22]	EMA position [38,39]
A stepwise approach to demonstrating biosimilarity	Recommended	Recommended
Preclinical evaluation of PK and PD	Recommended	Recommended
Comparative PK studies	Human studies required	Single-dose comparative human studies required
Comparative PD studies	Human studies recommended where clinically relevant markers available, but PK/PD may be assessed in parallel	Combine with PK studies, where a clinically relevant PD marker is available
Comparative clinical trials	At least one adequately powered equivalence trial in a population that allows for an assessment of clinically meaningful differences between the proposed product and the reference product	At least one adequately powered equivalence trial in the most sensitive patient population able to detect product-related differences, if present, and at the same time, reduce patient and disease-related factors to a minimum OR highly sensitive, dose-ranging PD studies may be sufficient
Safety	At least one adequately powered equivalence trial to demonstrate highly similar safety profiles. The population and duration of the comparative clinical study should allow for the detection of clinically meaningful differences between the two products	At least one adequately powered equivalence trial to demonstrate highly similar safety profiles in the most sensitive patient population able to detect product-related differences, if present, and at the same time, reduce patient and disease-related factors to a minimum
Immunogenicity	Required (included in safety study). The extent and timing of the clinical immunogenicity assessment will vary, depending on a range of factors, including the extent of analytical similarity between the proposed product and the reference product, and the incidence and clinical consequences of immune responses for the reference product	Required (included in safety study). A 12-month head-to-head comparative clinical study in which immunogenicity is compared between the biosimilar and reference product in the most sensitive population to detect potential differences is recommended for biosimilars intended for chronic treatment
Equivalence design with strict, predefined margins for clinical study	Recommended	Recommended

EMA, European Medicines Agency; FDA, US Food and Drug Administration; PD, pharmacodynamic; PK, pharmacokinetic.

regulatory approval for the EMA, FDA, and WHO (and those regulations that follow these) are very similar [5].

The global development of biosimilars can be characterized as a rapidly evolving landscape [10]. In 2005, the EMA was the first regulatory agency to establish a pathway for the development of biosimilars. Since then, the WHO and many countries have developed biosimilar guidelines. The following sections contain a brief overview of how these regulations came about and the current regulatory landscape.

EMA regulations

The European Union (EU) pioneered the development of regulatory requirements for biosimilars in 2005, when the EMA published a general framework guideline, introducing the principles of biosimilarity [52]. The EMA was also the first regulatory agency to give marketing authorization for biosimilars [5], from first-generation biologics (somatropin in 2006), erythropoietin (2007), and filgrastim (2008), to the first biosimilar mAb in 2013. As of October 23, 2015, the EMA website lists 19 licensed biosimilars, although it should be noted that this number includes multiple biosimilar versions of some of the same reference products [erythropoietin, somatropin (human growth hormone), and filgrastim] [17].

The extensive experience gained with licensed biosimilars has led to a robust regulatory process in the EU, with several guidelines issued and revised through time by the EMA, which include quality, nonclinical, and clinical aspects for the development of biosimilar mAbs [53,54], as well as a specific guideline for immunogenicity assessment [54]. Recent revisions led to the release of an updated overarching biosimilar guideline in 2013, which was adopted by the CHMP on October 2014 [20]. Originally, the EMA required the biosimilarity exercise to be conducted with a reference product licensed in the European Economic Area (EEA). The updated guidance states that in order to promote global development of biosimilars and avoid unnecessary clinical trials, certain clinical studies, and *in vivo* nonclinical studies may be alternatively conducted with non-EEA-authorized reference products (from a region with similar regulatory requirements), provided that both justification is provided and bridging studies are performed. Bridging data between the biosimilar candidate, the EEA-, and the non-EEA-authorized products should include analytical as well as PK and PD studies [20]. The regulatory framework in Europe continues to evolve as evidenced by a recent publication by Van Aerts et al. [55] that outlines a paradigm shift in regulatory thinking. This shift regards the limited use and, in many cases no use at all, of preclinical animal models for the characterization and evaluation of biosimilar mAbs and, by extension, other biosimilars.

Interchangeability and substitution remain key concerns regarding biosimilars. According to the European Generic and Biosimilar Medicines Association (EGA), interchangeability refers to the prescription of a biosimilar in place of the reference product by prescribers, while substitution means that pharmacists are allowed to dispense a biosimilar without the prescriber's knowledge or explicit request. Automatic substitution is used when the pharmacist is mandated by law to dispense the biosimilar in place of the originator. EMA regulatory guidelines do not include recommendations on interchangeability and substitution because decisions on these issues are regulated at the national level [56]. Most countries of the EU oppose automatic substitution of biosimilars, and many, such as Italy, Spain, and the UK, have enacted laws prohibiting the practice [57]. However, thinking around this issue is also evolving, as more information about biosimilars becomes available. This is evidenced by the recent reversal in opinion regarding switching from the Dutch Medicines Evaluation Board (MEB) as well as from France. Contrary to their previous

stance, the MEB now accepts interchangeability of biosimilars under certain conditions. Under the new guidance, switching between biologicals (whether originators or biosimilars) is permitted, but only if adequate clinical monitoring is performed and the patient is properly informed. In addition, MEB recommends that detailed product and batch information be recorded in the patient file in order to guarantee the traceability of the product [58]. France passed similar legislation in 2013 that allowed for substitution, albeit only under certain conditions such as whether a biosimilar can only be substituted for new patients and if the prescriber has not written "nonsubstitutable" [59].

Extrapolation of indications is another issue, influencing acceptance of biosimilars [40]. Many biological products used in rheumatology are approved for multiple indications. A key consideration for biosimilars is whether the clinical data obtained in a particular patient population may be extrapolated to support a determination of biosimilarity in other indications included in the reference product label [60]. The EMA requires that the applicant provide a scientific justification for extrapolation to all the licensed indications on the reference product label, based on the totality of evidence [20]. The EMA has ample experience concerning the extrapolation of indications. Commonly cited examples include the biosimilar filgrastim (reference product Neupogen) and epoetin. Several biosimilar filgrastims have been approved by the EMA for all indications of the reference product, based on extrapolation of data [17]; for example, Tevagrastim (2008) and Accofil (2014) were evaluated in one main study, each involving patients with breast cancer, but were approved for use in all indications included in the Neupogen label [61,62]. The efficacy and safety of these biosimilars have been subsequently confirmed by published reports from postmarketing studies [63]. Similarly, the first biosimilar mAb (infliximab) was also approved with extrapolation for all indications licensed for the reference product by the EMA in 2013 [17]. It is important to note, however, that different regulatory agencies have taken diverse stances on this issue. Health Canada, for example, approved biosimilar infliximab for most indications (including extrapolation of data to PsO) but did not grant extrapolation to IBD indications (Crohn's disease and ulcerative colitis) [63].

Safety is a key consideration for any medicine. Given the potential for differences in immunogenicity between the reference product and biosimilar (due to unavoidable differences described previously in this article) and that the rate of occurrence of AEs for biologics is low, it is not feasible to design a study that is adequately powered to fully detect differences in safety profile between both products [51]. Thus, as for all biologics, most regulatory agencies, including the EMA, require postmarketing surveillance for biosimilars as well. Under EMA guidance, pharmacovigilance and a risk management plan are expected to be proposed by the manufacturer at the time of application submission. The proposal should contain detailed information on risks and safety concerns, including immunogenicity data collection and detection of any new safety signals. In addition, the EMA encourages the use of registries and/or other large population studies. Further detail concerning pharmacovigilance programs as they relate to biosimilars is provided in earlier in this supplement series, "Evaluating Biosimilars for the Treatment of Chronic Inflammatory Diseases" [39,60,64]. To date, biosimilar epoetin and filgrastim annual periodic safety reports from the EMA have not yet identified differences in the safety profile of licensed biosimilars and their reference products [65].

WHO regulations

An important step in the harmonization of the evaluation and regulation of biosimilars took place in 2009, when WHO published

its “Guideline on evaluation of similar biotechnological products,” generally following the EMA’s scientific principles and requirements—that is, a stepwise comparability exercise approach with characterization of quality attributes of the product as the foundation, followed by nonclinical and clinical evaluations. Similar to the EMA guidelines, the amount of nonclinical and clinical data required is dependent upon the product class and evaluated on a case-by-case basis. WHO’s intent was to provide globally acceptable principles to license biosimilars of assured quality, safety, and efficacy based on a reduced clinical data package. Several countries have, in fact, adopted its principles in the development of their own regulatory requirements [16,25].

FDA regulations

Biosimilars cannot be considered generics and, thus, the current system of generic drugs in the United States, which was instituted with the enactment of the Hatch-Waxman Act [Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417)] is not appropriate for the evaluation and licensing of these products [1]. For this reason, and in an attempt to encourage the development of biosimilars, an abbreviated approval pathway for large biopharmaceuticals was established by the PPAC Act of 2010 [1], which will be described in detail below.

Before the enactment of the PPAC Act, the current system for evaluation of generic drugs, the Hatch-Waxman Act was enacted. The Act amended the Food, Drug, and Cosmetic (FD&C) Act to provide an abbreviated pathway—section 505(b)(2)—for the approval of generics, including natural source products and recombinant proteins. This abbreviated pathway allows for reliance, in part, on available knowledge about the safety and effectiveness of the already approved product, eliminating the need for replication of some preclinical and clinical studies [1,21]. Several simple proteins, such as natural bovine testicular and recombinant human hyaluronidase, recombinant salmon calcitonin, recombinant human glucagon, as well as the larger recombinant human somatropin, were approved by the FDA as generic drugs under section 505(b)(2) of the FD&C Act [1,21].

However, as mentioned above, because of the complexity of large protein products and the difficulty in demonstrating that the biosimilar product is identical to the reference product, it became clear this abbreviated approval pathway was insufficient for the evaluation and approval of more complex biologics [21]. Section 702 of the PPAC Act (also known as the Biologics Price Competition and Innovation Act of 2009) was then enacted to create an abbreviated Biologic License Application for “highly similar” biological products. Under this law, a biosimilar (termed “follow-on biological product” at the time) can be evaluated against only a single reference biological product, as long as it has the same mechanism of action, route of administration, dosage form(s), and potency as the reference product, and can only be approved for indications for which the FDA already has approved the reference product [50]. Since the enactment of the BPCI Act, the FDA has published a series of guidance documents to help with its implementation [66]. The first draft guidance issued in 2012 detailed the scientific principles underlying the determination of biosimilarity (totality of the evidence from a comprehensive stepwise comparability exercise) as well as the requirements for assessment by analytical methods between the biosimilar candidate and its reference product, and provided answers to common questions regarding the implementation of the BPCI Act [46,67,68]. In 2014, the FDA issued two additional draft guidance documents intended to further assist in the implementation of the BPCI Act. The first deals with the design of clinical pharmacology studies by PD and PK analyses, results from which guide the design of subsequent clinical trials to establish biosimilarity without

clinically meaningful differences and support extrapolation of clinical data [69]. The second is intended to clarify the requirements for the establishment of the appropriate exclusivity period (i.e., the definition of first licensing date of the reference products) during which a biosimilar application cannot be submitted and approved [44,69]. The FDA has also created a list of biologicals called the “Purple Book,” which includes information on exclusivity and expiration date of first licensure for biologicals licensed under section 351(a) of the PHS Act, as well as biosimilars with information of the reference product to which biosimilarity was demonstrated under section 351(k) of the PHS Act [70]. Finally, in 2015, a new draft guidance was issued that includes additional answers based on questions received by the FDA [71]. In April 2015, the FDA published final guidance documents for the initial three drafts issued in 2012 [66].

The first two biosimilars applications under section 351(k) of the PHS Act were filed in 2014: filgrastim by Sandoz [72] and infliximab by Celltrion [73]. On March 6, 2015, the FDA granted biosimilarity status (Sandoz did not request interchangeability status) and approval for the filgrastim produced by Sandoz [74].

Regarding interchangeability and substitution, the FDA’s interpretation differs somewhat from that of the EMA. According to the FDA, under the BPCI Act, a biological product is first approved as a biosimilar and may (or may not) then be determined to be “interchangeable” [22]. A biosimilar approved as interchangeable may be substituted for the reference product without the prescriber’s knowledge [50]. Contrary to the EU definition, in the United States, interchangeability is synonymous with automatic substitution. As such, determination of interchangeability will require a higher level of evidence. According to section 351(k) (4) of the PHS Act, “to meet the additional standard of ‘interchangeability,’ an applicant must provide sufficient information to demonstrate biosimilarity, and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk for safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch” [47]. However, the FDA has not yet established the required criteria that must be met to obtain such designation and has stated that it is unlikely any biosimilars will be designated as interchangeable medicines in the short term [22,71]. It is important to note that, regardless of the FDA’s designation, in the United States, legislation for automatic substitution is up to each state [75].

Regarding extrapolation of data to other indications, the FDA’s view is generally in line with that of the EMA as described above. The filgrastim biosimilar was unanimously recommended for all five indications granted to the reference product Neupogen by the Oncologic Drugs Advisory Committee and was approved for use in all 5 [76,77].

The FDA’s commitment to safety is also in line with that of the EMA. The FDA considers postmarketing safety monitoring to be “an important component in ensuring the safety and effectiveness of biological products, including biosimilars” [22]. Although specific pharmacovigilance requirements for biosimilars have not been specified, postmarketing reporting is mandatory for all products with unknown safety risks as specified in good pharmacovigilance practice guidance [78]. In addition to the known effectiveness and safety concerns associated with the reference product, the goals of the biosimilar pharmacovigilance program should be to identify and characterize any new AEs specific to the biosimilar and should be designed to differentiate between AEs associated with the biosimilar and those associated with the reference product. Biosimilar manufacturers are encouraged to

discuss plans for postmarketing surveillance with the FDA, which reserves the right to require additional postmarketing or clinical studies [22]. In addition, in the United States, any risk evaluation and mitigation strategies required of the reference product are applied to the biosimilar (per the BPCI Act) [50]. Of note, in an attempt to provide consumers and providers with greater confidence in biosimilars, the Academy of Managed Care Pharmacy convened a multidisciplinary task force to identify a system to monitor the safety and effectiveness of biosimilar products. The task force recommends the use of data consortia and suggests setting up an advisory council as the next necessary steps in the organization of a biosimilar-innovator intelligence system [79].

Regulations in other regions

Many highly regulated countries, including Japan, Korea, Canada, Australia, and New Zealand, have issued guidance documents and regulations that are generally in line with either WHO or EMA regulations (Fig. 3). Guidance documents from countries such as Canada or Korea share similar principles with those described in WHO regulations. In 2010, Health Canada, the federal regulatory authority responsible for the safety, efficacy, and quality evaluation of drugs, issued the “Guidance for Sponsors: Information and Submission Requirements for Subsequent Entry Biologics (SEBs),” to provide guidance on how to satisfy the regulatory requirements under the Canadian Food and Drugs Act and Regulations for the authorization of SEBs. This guidance explicitly states that Health Canada’s intention is to harmonize as much as possible with other competent regulators and international organizations [16].

In 2009, Korea defined a biosimilar as a biological product, that is, proven to be comparable in terms of quality, safety, and efficacy to an already marketed reference product in the “Guideline on Evaluation of Biosimilar Products” issued by the Korean Food and Drug Administration. This guidance was developed along with WHO regulations [16]. Other guidance documents, such as those issued in Australia in 2008 and Japan in 2009, are more closely aligned with EMA regulations [65].

Although some differences exist, they all share common key basic principles [80].

- (1) Same dose(s) and dosing regimen(s) as the reference product.
- (2) Demonstration of biosimilarity, and not re-establishment of benefit, is the cornerstone for biosimilar development: reduced clinical data package hinges on the demonstration of similar physicochemical and functional characteristics.
- (3) An extensive biosimilarity exercise at each step in the development process is required to establish similarity in quality, efficacy, and safety.

The interest in the biosimilars market is growing in the emerging markets due to a number of factors, including the burden that the high cost of imported branded biologics imposes on the healthcare budgets of many governments (e.g., as high as 50% in Brazil) [5]. Developing countries have long-treated copies of biologics primarily as generic equivalents [81]. As mentioned earlier, in many of these markets, these underregulated copies of some biologics have been manufactured, and even marketed as biosimilars [30,82,83]. Although the regulatory requirements in

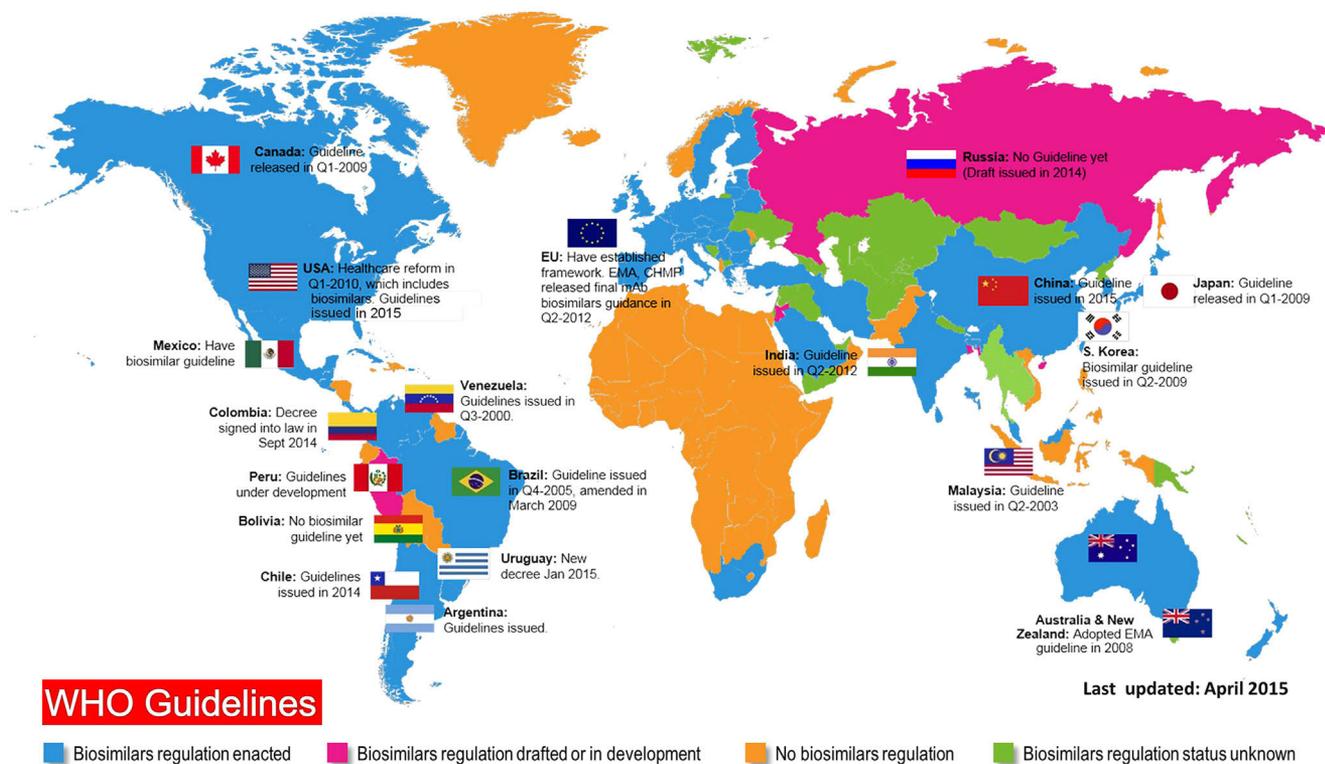


Fig. 3. Evolving landscape of the biosimilar regulatory pathways. The European Medicines Agency (EMA) pioneered the development of a regulatory framework for the development and approval of biosimilars [16]. In an attempt to harmonize regulations worldwide, the World Health Organization (WHO) issued guidelines following very similar principles to those of the EMA [5], and many countries based their regulatory requirements on the principles established by these guidelines [16,25]. Currently, many developed countries have rigorous regulatory processes that ensure comparability of biosimilars with their reference products [82]. Although regulations vary substantially across countries, many countries are striving toward harmonization of accepted criteria, such as those set forth by the EMA, the US Food and Drug Administration, and the WHO. Some countries in the Latin American region specifically are moving toward more rigorous oversight generally based on accepted international standards [82]. However, there is still a lack of a uniform approach to the regulatory approval and in some countries synthetic copies of brand compounds have been approved without comparative clinical studies with the innovator [31].

some of these countries are less rigorous than WHO, EMA, or FDA regulations, many countries are now developing more stringent regulations for the development and approval of biosimilars [81,82]. Some of these legacy products approved under generics criteria in international markets could potentially become biosimilars, as the experienced producers of these products upgrade their biomanufacturing process and conduct needed trials to meet biosimilar standards of highly developed countries [81].

Several countries (e.g., China and Brazil) now require the domestic manufacture of their domestically approved biopharmaceuticals [81]. For example, the Brazilian government created a program in 2012, updated in 2014, whereby a local partner is critical to do business in Brazil. The agreements between local companies and large private multinationals are called partnerships for product development (PDPs). A PDP is required for biosimilar submission. The private companies should eventually fully transfer the technology to the public partners and, in exchange, the government guarantees purchase for 5 years for provision of the Unified Health System. The objective of the program is to improve its biotechnology and biomanufacturing capabilities and locally manufacture its own biosimilars [5].

However, lack of harmonization and the management of previously approved nonconforming products remain issues of concern [82,83]. For these reasons, and in order to help ensure the efficacy and safety of biosimilars, there have been calls for the development of effective postmarketing surveillance programs that will ultimately determine the efficacy and safety of the biosimilar and confirm its similarity to the reference product. For example, to aid policy makers in Latin America in addressing the significant difficulties encountered in the development and implementation of robust pharmacovigilance systems, in countries where few AEs are reported [83], the Americas Health Foundation convened a group of experts who recently published recommendations for the implementation of such systems [84].

Summary and conclusions

Although biologic therapy is indicated for the treatment of numerous chronic inflammatory diseases, access to this therapeutic modality may be limited. The addition of biosimilars to the market may improve access to such treatments by increasing the number of biologic drugs available. Though the regulatory landscape concerning biosimilar development and approval is varied across different regions of the world, many countries are striving toward harmonization of accepted criteria, such as those set forth by the EMA, FDA, and WHO, which have established comparable principles and guidelines defining biosimilars and stringent processes required to develop and license a biosimilar. By undergoing the rigorous process of early-stage analytical, structural, and functional comparative analyses between the biosimilar and originator product, the corresponding clinical data package may be tailored while maintaining the quality, efficacy, and safety of the biosimilar.

References

- [1] Kay J. Biosimilars: a regulatory perspective from America. *Arthritis Res Ther* 2011;13:1–5.
- [2] Kanter J, Feldman R. Understanding and incentivizing biosimilars. *Hastings Law J* 2012;64:57–83.
- [3] Dörner T, Strand V, Castañeda-Hernández G, Ferraccioli G, Isaacs JD, Kvien TK, et al. The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis* 2013;72:322–8.
- [4] Johnson IS. Human insulin from recombinant DNA technology. *Science* 1983;219:632–7.
- [5] Tsuruta LR, Lopes Dos Santos M, Moro AM. Biosimilars advancements: moving on to the future. *Biotechnol Prog* 2015;31:1139–49.
- [6] Schett G, Elewaut D, McInnes IB, Dayer JM, Neurath MF. How cytokine networks fuel inflammation: toward a cytokine-based disease taxonomy. *Nat Med* 2013;19:822–4.
- [7] Nast A, Rosumeck S, Seidenschner K. Biosimilars: a systematic review of published and ongoing clinical trials of antipsoriatics in chronic inflammatory diseases. *J Dtsch Dermatol Ges* 2015;13:294–300.
- [8] Amiot A, Peyrin-Biroulet L. Current, new, and future biological agents on the horizon for the treatment of inflammatory bowel diseases. *Therap Adv Gastroenterol* 2015;8:66–82.
- [9] Strand V, Smith J. Introduction of a biologic agent into the clinic. In: Weismaan MH, Weinblatt ME, Louie JS, van Vollenhoven RF, editors. *Targeted treatment of the rheumatic diseases*. Philadelphia, PA: Elsevier; 2010.
- [10] Scheinberg MA, Kay J. The advent of biosimilar therapies in rheumatology—“O Brave New World”. *Nat Rev Rheumatol* 2012;8:430–6.
- [11] Smolen JS, Landewé R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014;73:492–509.
- [12] Agarwal SK. Core management principles in rheumatoid arthritis to help guide managed care professionals. *J Manag Care Pharm* 2011;17:S3–8.
- [13] Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. *Arthritis Care Res* 2012;64:625–39.
- [14] Lichtenstein GR, Hanauer SB, Sandborn VJ. Practice parameters committee of American College of gastroenterology. Management of Crohn's disease in adults. *Am J Gastroenterol* 2009;104:465–83.
- [15] Kornbluth A, Sachar DB. Practice parameters committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010;105:501–23.
- [16] Wang J, Chow SC. On the regulatory approval pathway of biosimilar products. *Pharmaceuticals*, 5; 2012, 353–68.
- [17] European Medicines Agency. European public assessment reports-biosimilars. (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&searchTab=searchByAuthType&keyword=Enter_keywords&searchType=name&alreadyLoaded=true&status=Authorised&status=Withdrawn&status=Suspended&status=Refused&jsenabled=false&searchGenericType=biosimilars&orderBy=authDate&pageNo=1) [accessed 22.10.15].
- [18] Thorpe R, Wadhwa M. Terminology for biosimilars—a confusing minefield. *Gabi J* 2012;1:132–4. (<http://gabi-journal.net/terminology-for-biosimilars-a-confusing-minefield.html>) [accessed 15.06.15].
- [19] Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Narayanan G, et al. Biosimilars—why terminology matters. *Nat Biotechnol* 2011;29:690–3.
- [20] European Medicines Agency. Guideline on similar biological medicinal products. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf); 2014 [accessed 15.06.15].
- [21] Woodcock J, Griffin J, Behrman R, Cherney B, Crescenzi T, Fraser B, et al. The FDA's assessment of follow-on protein products: a historical perspective. *Nat Rev Drug Discov* 2007;6:437–42.
- [22] U.S. Food and Drug Administration. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf>); 2015 [accessed 15.06.15].
- [23] Health Canada. Guidance for sponsors: information and submission requirements for Subsequent Entry Biologics (SEBs) Minister of Public Works and Government Services Canada. (http://www.hc-sc.gc.ca/dhp-mps/alt_formats/pdf/brgtherap/applic-demande/guides/seb-pbu/seb-pbu-2010-eng.pdf); 2010 [accessed 30.06.15].
- [24] López Silva C. Mexico recovers leadership on regulation of biosimilar biotech drugs. *Gac Med Mex* 2012;148:83–90 [Spanish].
- [25] World Health Organization. Guidelines on evaluation of similar biotherapeutic products (SBPs). (http://www.who.int/biologicals/areas/biological_therapeutics/BIO_THERAPEUTICS_FOR_WEB_22APRIL2010.pdf); 2009 [accessed 15.06.15].
- [26] Pitts PJ, Stark R. Biosimilars. The precarious struggle between cost-driven health care policy and patient-centered care. Washington, DC: Washington Policy Center; 2012.
- [27] Beck A. Biosimilar, biobetter and next generation therapeutic antibodies. *MAbs* 2011;3:107–10.
- [28] Van de Vooren K, Curto A, Garattini L. Biosimilar versus generic drugs: same but different. *Appl Health Econ Health Policy* 2015;13:125–7.
- [29] International Federation of Pharmaceutical Manufacturers & Associations. Noncomparable biotherapeutic products: policy statement. (http://www.ifpma.org/uploads/media/Non-comparable_Biotherapeutic_Products_English_06.pdf); 2014 [accessed 30.06.15].
- [30] Strand V, Brasington R. A biologic by any other name. *Rheumatologist* 2013;7:20–1.
- [31] Scheinberg M, Castañeda-Hernández G. Anti-tumor necrosis factor patent expiration and the risks of biocopies in clinical practice. *Arthritis Res Ther* 2014;16(6):501.
- [32] Barile-Fabris L, Irazoque-Palazuelos F, Hernández Vásquez R, Carrillo Vazquez S, Guzman R. Incidence of adverse events in patients treated with intended copies of biologic therapeutic agents in Colombia and Mexico. Poster 1506. American College of Rheumatology Annual Meeting; 2014.
- [33] Ryan AM. Frontiers in nonclinical drug development: biosimilars. *Vet Pathol* 2015;52:419–26.
- [34] Gece KB, Khanna R, van den Brink GR, Ponsioen CY, Löwenberg M, Jairath V, et al. Biosimilars in IBD: hope or expectation. *Gut* 2013;62:803–7.
- [35] Schellekens H. Biosimilar therapeutics—what do we need to consider? *NDT Plus* 2009;2(Suppl. 1):i27–36.

- [36] Dranitsaris G, Dorward K, Hatzimichael E, Amir E. Clinical trial design in biosimilar drug development. *Invest New Drugs* 2013;31:479–87.
- [37] Declerck PJ. Biosimilar monoclonal antibodies: a science-based regulatory challenge. *Expert Opin Biol Ther* 2013;13:153–6.
- [38] European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf); 2014 [accessed 28.07.15].
- [39] European Medicines Agency. Guideline on similar biological medicinal products containing monoclonal antibodies—non-clinical and clinical issues. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128686.pdf); 2012 [accessed 15.06.15].
- [40] Weise M, Bielsky MC, De Smet K, Ehmann F, Ekman N, Giezen TJ, et al. Biosimilars: what clinicians should know. *Blood* 2012;120:5111–7.
- [41] Wroblewski MS, Jex EA, Munck SD, Garmon CJ, Michel ST, Wantman A, et al. Emerging health care issues: follow-on biologic drug competition. US Federal Trade Commission. (<http://www.ftc.gov/sites/default/files/documents/reports/emerging-health-care-issues-follow-biologic-drug-competition-federal-trade-commission-report/p083901biologicsreport.pdf>); 2009 [accessed 15.06.15].
- [42] Gupta D, Prashanth GN, Lodha SA. CMO perspective on quality challenges for biopharmaceuticals. *BioProcess Int* 2013;11:22–6. (<http://www.bioprocessintl.com/manufacturing/antibody-non-antibody/a-cmo-perspective-on-quality-challenges-for-biopharmaceuticals-347335/>).
- [43] US Food and Drug Administration. Guidance for industry: clinical development programs for drugs, devices, and biological products for the treatment of rheumatoid arthritis (RA). (<http://www.fda.gov/downloads/Drugs/Guidances/ucm071579.pdf>); 1999 [accessed 15.06.15].
- [44] U.S. Food and Drug Administration. Draft guidance for industry: reference product exclusivity for biological products filed under section 351(a) of the PHS Act. (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm407844.pdf>); 2014 [accessed 15.06.15].
- [45] US Food and Drug Administration. Guidance for industry: quality considerations in demonstrating biosimilarity to a reference protein product. (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291134.pdf>); 2015 [accessed 15.06.15].
- [46] US Food and Drug Administration. Draft guidance for industry: biosimilars: questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM273001.pdf>); revised May 2015 [accessed 15.06.15].
- [47] US Food and Drug Administration. Guidance for industry: biosimilars: additional questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444661.pdf>); 2015 [accessed 15.06.15].
- [48] Galbraith D. Biosimilars awaken CROs. *BioProcess Int* 2014;12(Suppl. 6):s24–7.
- [49] McCamish M, Woollett G. The state of the art in the development of biosimilars. *Clin Pharmacol Ther* 2012;91:405–17.
- [50] Congress of the United States of America. Biologics Price Competition and Innovation Act. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf>); 2009 [accessed 15.06.15].
- [51] Strand V, Cronstein B. Biosimilars: how similar. *Intern Med J* 2014;44:218–23.
- [52] European Medicines Agency. Guideline on similar biological medicinal products. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf); 2005 [accessed 15.06.15].
- [53] European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues (revision 1). (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/06/WC500167838.pdf); 2014 [accessed 15.06.15].
- [54] European Medicines Agency. Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use. (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500128688.pdf); 2012 [accessed 15.06.15].
- [55] Van Aerts LA, De Smet K, Reichmann G, van der Laan JW, Schneider CK. Biosimilars entering the clinic without animal studies: a paradigm shift in the European Union. *MAbs* 2014;6:1155–62.
- [56] European Generic Medicines Association. Biosimilars handbook. (http://www.egagenics.com/images/Website/EGA_BIOSIMILARS_handbook_en.pdf) [accessed 15.06.15].
- [57] Rovira J, Espín J, García L, Olry de Labry A. The impact of biosimilars' entry in the EU market. (<http://ec.europa.eu/DocsRoom/documents/7651/attachments/1/translations/en/renditions/pdf>); 2011 [accessed 12.02.16].
- [58] Netherlands Medicines Evaluation Board. News item. Clarification of stance on biological and biosimilar medicines. (<http://english.cbg-meb.nl/latest/news/2015/08/17/clarification-of-stance-on-biological-and-biosimilar-medicines>); 17.08.15 [accessed 24.09.15].
- [59] Taylor L. France moving ahead with biosimilar substitution. *PharmaTimes Digital*. (http://www.pharmatimes.com/Article/14-04-13/France_moving_ahead_with_biosimilar_substitution.aspx); 2014 [accessed 12.02.16].
- [60] Feldman SR. Inflammatory diseases: integrating biosimilars into clinical practice. *Semin Arthritis Rheum* 2015;44(6 Suppl.):s16–21.
- [61] European Medicines Agency. Assessment Report. Tevagrastim. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/000827/WC500036667.pdf); 2008 [accessed 15.06.15].
- [62] European Medicines Agency. Assessment Report. Accofil. (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003956/WC500176640.pdf); 2014 [accessed 15.06.15].
- [63] Weise M, Kurki P, Wolff-Holz E, Bielsky MC, Schneider CK. Biosimilars: the science of extrapolation. *Blood* 2014;124:3191–6.
- [64] Reinisch W, Smolen J. Biosimilar safety factors in clinical practice. *Semin Arthritis Rheum* 2015;44(Suppl. 6):s9–15.
- [65] Bennett CL, Chen B, Hermanson T, Wyatt MD, Schulz RM, Georgantopoulos P, et al. Regulatory and clinical considerations for biosimilar oncology drugs. *Lancet Oncol* 2014;15:e594–605.
- [66] US Food and Drug Administration. Biosimilars guidances. (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm>); [accessed 15.06.15].
- [67] US Food and Drug Administration. Draft guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>); 2012 [accessed 15.06.15].
- [68] US Food and Drug Administration. Draft guidance for industry: quality considerations in demonstrating biosimilarity to a reference protein product. (<http://www.pitdc.org.tw/member/%E5%90%84%E5%9C%8B%E6%B3%95%E8%A6%8F/USA/Quality%20Considerations%20in%20Demonstrating%20Biosimilarity%20to%20a%20Reference%20Protein%20Product.pdf>); 2012 [accessed 21.10.15].
- [69] US Food and Drug Administration. Draft guidance for industry: clinical pharmacology data to support a demonstration of biosimilarity to a reference product. (<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf>); 2014 [accessed 15.06.15].
- [70] US Food and Drug Administration. Background information: lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations (purple book). (<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalsApplications/TherapeuticBiologicApplications/Biosimilars/ucm411424.htm>). Updated March 2015 [accessed 15.06.15].
- [71] US Food and Drug Administration. Draft guidance for industry. Biosimilars: Additional questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. (<http://www.fda.gov/downloads/Drugs/Guidances/UCM273001.pdf>); 2015 [accessed 15.06.15].
- [72] Sandoz Press Release. FDA accepts Sandoz application for biosimilar filgrastim. (http://www.sandoz.com/media_center/press_releases_news/global_news/2014_07_24_FDA_accepts_Sandoz_application_for_biosimilar_filgrastim.shtml); 2014 [accessed 15.06.15].
- [73] Celltrion Press Release. Celltrion files for US FDA approval of Remsima[®]. (http://www.celltrion.com/en/company/notice_view.asp?id=456&code=enews&intNowPage=1&menu_num=align_year=all); 2014 [accessed 15.06.15].
- [74] US Food and Drug Administration [press release]. FDA approves first biosimilar product Zarxio. (<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm436648.htm>); 2015 [accessed 15.06.15].
- [75] National Conference of State Legislatures. State laws and legislation related to biologic medications and substitution of biosimilars. (http://www.ncsl.org/documents/health/BiosimilarsNCSLReport_July_2014.pdf); 2014 [accessed 15.06.15].
- [76] US Food and Drug Administration. Center for drug evaluation and research summary minutes of the Oncologic Drugs Advisory Committee Meeting January 7, 2015. (<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM436385.pdf>); Published January 2015 [accessed 24.09.15].
- [77] ZARXIO[™] (filgrastim-sndz) Full Prescribing Information. Princeton, NJ: Sandoz Inc.
- [78] US Food and Drug Administration. Guidance for industry: good pharmacovigilance practices and pharmacoepidemiologic assessment. (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126834.pdf>); 2005 [accessed 15.06.15].
- [79] Baldziki M, Brown J, Chan H, Cheetham TC, Conn T, Daniel GW, et al. For the AMCP Task Force on Biosimilar Collective Intelligence Systems. Utilizing data consortia to monitor safety and effectiveness of biosimilars and their innovator products. *J Manag Care Spec Pharm* 2015;21:23–34.
- [80] Derbyshire M. Comparison of biosimilars guidelines. *GaBI J* 2014;3:36–8.
- [81] Rader RA. Biosimilars in the rest of the world: developments in lesser-regulated countries. *BioProcess J* 2014;12:41–7.
- [82] Castañeda-Hernández G, Szekanez Z, Mysler E, Azevedo VF, Guzman R, Gutierrez M, et al. Biopharmaceuticals for rheumatic diseases in Latin America, Europe, Russia, and India: innovators, biosimilars, and intended copies. *Joint Bone Spine* 2014;81:471–7.
- [83] Azevedo VF, Mysler E, Aceituno Álvarez A, Hughes J, Flores-Murrieta FJ, Ruiz de Castilla EM. Recommendations for the regulation of biosimilars and their implementation in Latin America. *GaBI J* 2014;3:143–8.
- [84] Pineda C, Caballero-Urbe CV, de Oliveira MG, Lipszyc PS, Lopez JJ, Mataos Moreira MM, et al. Recommendations on how to ensure the safety and effectiveness of biosimilars in Latin America: a point of view. *Clin Rheumatol* 2015;34:635–40.
- [85] National Institutes of Health. Methotrexate. Pub Chem Compound Summary for CID 126941. (<https://pubchem.ncbi.nlm.nih.gov/compound/methotrexate#section=Top>) [accessed 01.07.15].
- [86] Kozlowski S, Woodcock J, Midthun K, Sherman RB. Developing the nation's biosimilars program. *N Engl J Med* 2011;365:385–8.
- [87] US Government Publishing Office. 42 U.S.C. 262—Regulation of biological products. (<http://www.gpo.gov/fdsys/pkg/USCODE-2010-title42/pdf/USCODE-2010-title42-chap6A-subchap1-partf-subpart1-sec262.pdf>) [accessed 25.09.15].
- [88] US Government Publishing Office. 21 U.S.C. 355—New drugs. (<http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/pdf/USCODE-2010-title21-chap9-subchapV-partA-sec355.pdf>) [accessed 25.09.15].