Seminars in Arthritis and Rheumatism 44 (2015) S9–S15

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Biosimilar safety factors in clinical practice

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ARTICLE INFO

Keywords:
Chronic inflammatory diseases
Biosimilar
biologic
reference product
chronic inflammatory diseases
safety
interchangeability
comparability
immunogenicity
extrapolation
pharmacokinetics
pharmacodynamics
pharmacovigilance/surveillance
regulatory requirements
naming/labeling

ABSTRACT

Objectives: This article provides insight into the guidelines issued by the European Medicines Agency (EMA) and the draft guidances issued by the US Food and Drug Administration (FDA) regarding potential safety considerations associated with the development and use of biosimilars.
Methods: EMA and FDA guidelines and the literature were reviewed to identify recommendations and experience of manufacturers regarding the safety of biosimilars.
Results: Recent results of phase 3 comparability clinical trials comparing biosimilars with their reference products, and the approval of a biosimilar infliximab by several regulatory agencies, demonstrate the growing importance of biosimilars in inflammatory diseases. The safety profiles of biosimilars developed according to regulatory guidelines appear to be highly similar to the reference product, and postmarketing pharmacovigilance programs are in place. Additional topics related to biosimilars, such as interchangeability, automatic substitution, and nomenclature, are discussed.
Conclusions: Safety considerations in the development of biosimilars are an important focus of regulatory guidelines, although topics such as interchangeability, automatic substitution, and nomenclature are still being debated.

Introduction

More than 15 years ago, the first of many monoclonal antibodies that target pro-inflammatory cytokines became available. These agents have become standard-of-care options for the treatment of inflammatory diseases such as rheumatoid arthritis (RA), psoriasis (PsO), psoriatic arthritis (PsA), Crohn's disease (CD), and ankylosing spondylitis (AS) [1–3]. As the patents of infliximab and other biologic products used for inflammatory diseases have expired in some countries in Europe and will soon expire in the rest of the European Union (EU) and the United States, the development of biosimilar agents is rapidly moving forward [1,4]. A biosimilar infliximab was first approved for various inflammatory diseases in South Korea, then the EU, and recently in Canada, Colombia, India, Japan, Turkey, and other countries to be marketed under the trade names Remsima and Inflectra [5–9].

Several reasons exist for interest in the development of biosimilars by industry and society. Biosimilar compounds are being developed to address the needs of health care stakeholders, reduce health care costs, and also to potentially increase patient access to the biologic class of therapies that already have broad penetration within the treatment landscape [10]. A recent analysis by IMS Health showed that, among 21 European countries, the median price for erythropoietin (weighted based on the market share of the biosimilar) declined 35% from 2006 to 2013 [11].

An important focus of the development of biosimilars is safety. Developing a biosimilar with a safety profile similar to the reference product can be challenging due to the complex molecular structure and complicated manufacturing process involved. In addition, the molecular structure of biologic products also is sensitive to changes in formulation, packaging, and storage. Safety considerations include immunogenicity, hypersensitivity reactions, and an increased risk for other adverse effects [12–16].

This article provides insight into the guidelines issued by the EMA and the draft guidances issued by the US Food and Drug Administration (FDA) regarding potential safety considerations associated with the development and postmarketing use of biosimilars. The EMA and FDA principles regarding safety considerations are similar (Table) [17–20].

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http://dx.doi.org/10.1016/j.semarthrit.2015.04.005

Table
Comparison of EMA guidelines and FDA guidances regarding safety related to biosimilars for inflammatory disease

EMA	FDA
Risks of particular interest	
Infusion-related reactions, immunogenicity [17]	Immunogenicity [19]
Immunogenicity testing	
Use same assay format and sampling schedule for biosimilar and reference product	A multitiered testing approach beginning with a screening assay is recommended
Perform in blinded, parallel fashion	Use same assay format and sampling schedule for biosimilar and reference product
Low doses, if medically possible, provide a more sensitive comparison of immune response[17,18]	The assay should not be affected by the presence of rheumatoid factor, IgM, or anti-IgG
1-year follow-up data generally required before approval [17,18]	Perform in parallel fashion; a one-sided design generally is adequate
	Select dose on steepest part of the dose-response curve
	1-year follow-up data generally required before approval [19,20]
Extrapolation	
Justify or demonstrate for each claimed indication [17]	Justify for each claimed indication
	Use population and treatment regimens that are the most sensitive for detecting a difference [19]
Pharmacovigilance	
Required postmarketing	Postmarketing may be required
Based on identified/potential risks of reference product and potential risks identified with biosimilar	Based on identified risks of the reference product or its class and biosimilar. Adequate mechanisms should be in place to differentiate adverse events associated with the reference product and approved biosimilar [19]
Participate in existing pharmacoepidemiologic and risk minimization activities for the reference product	
Consider possibility of switching and interchanging [17]	
Labeling	
–	Include all information necessary for health care professional to make prescribing decisions[19]

Biosimilars from development to delivery: Implications for safety

A fundamental regulatory requirement of biosimilarity is that there are no clinically meaningful differences between the biologic product (i.e., biosimilar) and the reference product in terms of quality, safety, and efficacy [17,21]. A "biosimilar" that does not meet this standard cannot be approved as a biosimilar. Clearly patient safety is a key consideration throughout the step-wise development of a biosimilar in the United States and EU that continues through postmarketing safety monitoring [19].

Immunogenicity

Because biologic products, including monoclonal antibodies, by their very nature are capable of eliciting immune responses in humans, immunogenicity is a focus of safety assessments during development. An immune response may lead to altered efficacy or compromised safety (Fig. 1) [22–24]. Specific effects of immune responses include (1) an immune response that may include immune complex formation [25] resulting in (2) decreased or increased clearance of the biologic [26] and (3) neutralization of the activity of the biologic [22,23].

Subtle changes in manufacturing, purification, or packaging, as well as shipping and storage conditions, have the potential to impact the molecular structure of the biologic product and, hence, its immunogenic potential [12,15,23,27–29]. Immunogenicity also can be impacted by the dose, formulation, and route of administration, as well as individual patient factors such as atopy and immunosuppression [12,22,24].

Biologics, including monoclonal antibodies, are capable of inducing two types of antidrug antibodies (ADAbs), neutralizing and non-neutralizing antibodies, both of which have the potential to compromise efficacy and safety [20,22,24,25]. Neutralizing antibodies may cross-react with an endogenous counterpart of the biologic or related biologics, thereby adversely affecting its safety or reducing efficacy [19]. Cross-reacting with a non-redundant counterpart can have severe, immediate consequences, while cross-reacting with a redundant counterpart may not produce an obvious clinical syndrome until a stressful event occurs [25,26].

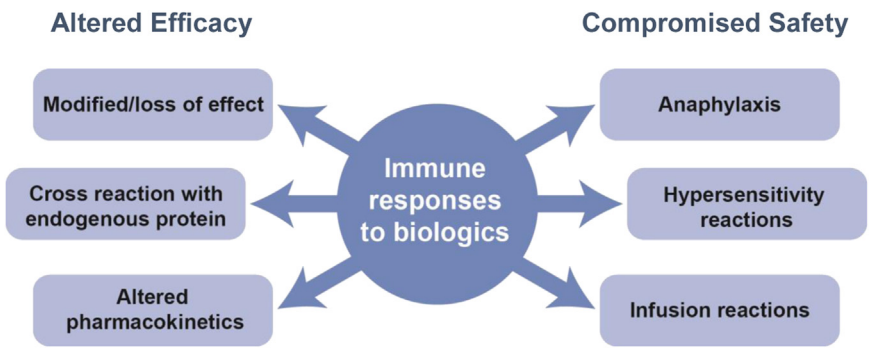

Fig. 1. Immune response can influence efficacy and safety of a biologic [22–24].

Non-neutralizing antibodies may alter efficacy by diminishing or enhancing the pharmacokinetics (PK) of the biologic or by mistargeting the biologic into FC receptor bearing cells. Non-neutralizing antibodies also may promote the generation of neutralizing antibodies via epitope spreading [26].

The extent of reduced biologic response due to ADAbs was demonstrated in a recent meta-analysis of 12 prospective studies involving 865 patients with RA, AS, PsO, or inflammatory bowel disease who received infliximab or adalimumab [30]. Overall, detectable ADAbs reduced the response rate to the biologic (adalimumab or infliximab) by 68% [risk ratio (RR): 0.32, 95% confidence interval (CI): 0.22–0.48]. However, the overlap between responders with and without ADAbs and nonresponders with and without ADAbs was substantial [31]. Therefore, it is not clear to what extent ADAb levels affected clinical response. Moreover, recent observational studies have shown that certain drugs that elicit ADAb response demonstrated better response rates than those that did not, questioning the importance of ADAb determination in the clinic [32].

The development of ADAbs and their clinical impact is affected by concomitant immunosuppressive therapy. It has long been known that, at least in RA, the presence of methotrexate and other conventional synthetic disease-modifying anti-rheumatic drugs (DMARDs) reduce the frequency of neutralizing antibodies [33]. The dose of methotrexate that is sufficient to inhibit ADAb formation may be 7.5–10 mg or lower [33–35]. Where the proportion of patients co-treated with immunosuppressive therapy was $<67\%$, detectable ADAbs were associated with a reduction in therapeutic response to the biologic by 78% (adalimumab and infliximab combined) (RR: 0.22, 95% CI: 0.12–0.39) [30]. This is in contrast to a reduction of 59% where the proportion of patients co-treated with immunosuppressive therapy was $\geq 67\%$ (RR: 0.41, 95% CI: 0.27–0.62). These results demonstrate an improved therapeutic response that may or may not be related to lower ADAb levels in those with greater use of immunosuppressive therapy [30].

Other safety considerations, in addition to immunogenicity include adverse events such as infusion or injection site reactions, hepatotoxicity, neutropenia, fever, and infection [24,25].

Manufacturing

Because even small alterations in the source materials or production process of any biologic product may lead to changes in molecular structure, and potentially its biologic effects, manufacturing processes are carefully controlled at each step (Fig. 2) [1,3,36]. Post-translational modifications of the tertiary or quaternary structure such as glycosylation (sugar moieties), methylation, oxidation, and deamidation are among the most common observed with changes in manufacturing. Such modifications can affect the binding affinity, PK, Fc receptor function, and immunogenicity of monoclonal antibodies [1,3,36,37].

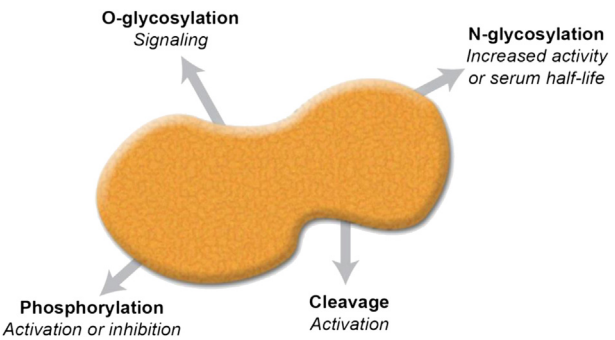

Fig. 2. Examples of post-translational modifications and their functional effects [36].

During development of the biosimilar, it is critical that not only the primary amino acid sequences but also higher-order structures be reproduced to the greatest extent possible. This is an important consideration for the biosimilar manufacturer given the proprietary (and usually confidential) nature of the original manufacturing process of the reference product, as well as subsequent changes [3]. Nevertheless, even manufacturers of reference products may encounter significant batch-to-batch variations [1,3,36,37].

Safety also can be compromised by process-related impurities from cell substrates (e.g., host cell DNA and host cell proteins), cell culture components (e.g., antibiotics and media components), and downstream processing steps (e.g., reagents, residual solvents, leachables, endotoxins, and bioburden). Analytical procedures are implemented to detect, identify, and accurately quantify biologically significant levels of impurities. Safety with regard to unexpected agents or endogenous viral contamination is undertaken by screening critical raw materials and the use of processes for robust virus removal and inactivation during manufacturing [38]. Thus, as with all biologics, adherence to stringent manufacturing practices consistent with FDA and EMA requirements is essential for manufacturers of reference products as well as biosimilars.

Formulation and packaging

Formulation differences of the biosimilar relative to the reference product are permitted provided the manufacturer of the biosimilar submits evidence demonstrating the differences are not clinically meaningful [18,19]. Clinically meaningful differences could include a difference in the expected range of safety, purity, and potency between the biosimilar and reference product, whereas slight differences in rates of occurrence of adverse events would not be considered clinically meaningful, and even could occur between studies of the same reference product [19]. In its assessment of the biosimilar infliximab, the EMA noted that the incidence of adverse events observed with the biosimilar and reference product generally were similar but a postmarketing monitoring program has been approved by the EMA. Serious infections as well as rare adverse events known to the reference product, such as malignancies and lymphoproliferative disorders, will be closely monitored as part of the postmarketing risk management plan. One common component of postmarketing monitoring is the use of registries, which often include different patient populations. In addition to existing biologic registries such as the British Society for Rheumatology Biologics Register-Rheumatoid Arthritis (BSRBR-RA), the Rheumatoid Arthritis Observation of Biologic Therapy (RABBIT), and others, biosimilar-specific registries also may be part of the postmarketing surveillance program [5,6]. In the United States, as for any other biologic, the FDA may require additional postmarketing studies to ensure the product's safety and effectiveness [19].

Regulatory guidelines regarding safety of biosimilars

Preclinical studies

Preclinical studies help resolve uncertainties regarding biosimilarity that remain following extensive structural and functional investigations. Although they do not replace clinical studies in humans, preclinical studies using animal models may be useful to preliminarily assess toxicity, including immunogenicity. Experience with the reference product and available information on the reference product serve to inform preclinical studies [19].

When animal toxicity studies are conducted, the selection of dose, regimen, duration, and test species should provide a meaningful toxicological comparison between the biosimilar and reference product.

It is important to understand the limitations of such animal studies when interpreting the results of preclinical studies. These include small sample size and intraspecies variations [19].

Clinical studies

The development of a biosimilar must include one or more clinical studies, including an assessment of immunogenicity and PK or pharmacodynamics (PD). The study(ies) must be sufficient to demonstrate similar safety in one or more appropriate conditions for which the reference product is licensed and intended to be used, and for which licensure of the biosimilar is sought [19,39]. During the design of the clinical study extrapolation of data to several indications should be taken into consideration, in particular the selection of the patient population (extrapolation is examined further in this supplement). Beyond unresolved safety issues from nonclinical development, clinical experience with the reference product and its therapeutic class inform the nature and extent of clinical development [19].

Because it is not feasible to design a clinical trial for statistical comparison of adverse events, the clinical study must be designed to allow a detailed comparison of the adverse events reported with the reference product and its class, or those identified during PK/PD evaluation of the biosimilar. Safety information from the clinical study(ies), coupled with preclinical development, comprise the safety profile of the biosimilar and is generally adequate for demonstrating similarity [40]. However, the relatively small number of patients included in the clinical study generally precludes detecting differences in rare adverse events between the biosimilar and reference product. These can be addressed with postmarketing pharmacovigilance programs. In addition to immune-mediated events, adverse events include those related to an exaggerated pharmacology of the biologic such as infection in the case of tumor necrosis factor alpha inhibitors or other safety issues such as heart failure, systemic lupus erythematosus, hepatobiliary events, and hematologic reactions [5,6,40].

Immunogenicity has been a key safety end point in the clinical development of all biosimilars. For example, with the recently approved biosimilar infliximab, used in patients with RA or AS, the incidence of antibody development has been shown to be similar with the reference product in phase 3 clinical trials [41–43]. Moreover, this apparently continued to be the case when patients were switched from reference infliximab to biosimilar infliximab [44]. Overall, the incidence and severity of adverse events were similar with biosimilar infliximab and reference infliximab [41,42].

Immunogenicity

The goal of the clinical immunogenicity assessment is to evaluate potential differences between the biosimilar and the reference product in the incidence and impact of the human immune response [19,45]. The extent and timing (e.g., premarket versus pre- and post-market testing) of the assessment of clinical immunogenicity vary depending on findings from nonclinical development of the biosimilar and experience with the reference product [19]. Both FDA and EMA require pre-approval immunogenicity testing but differ in their requirements for postmarketing assessment. EMA requires that immunogenicity be addressed during the required post-market pharmacovigilance program, while the FDA states that rare, but potentially serious, safety risks, including immunogenicity may require evaluation through postmarketing surveillance [18,19]. A head-to-head study is used to consider the severity of consequences and the incidence of immune responses. In addition, because it is only important to demonstrate that the immunogenicity of the biosimilar is not increased relative to the reference product, a one-sided design usually is used [19]. The one-sided design utilizes an upper limit for the incidence of immunogenicity based on experience with the reference product. A lower limit is not utilized since it is acceptable for the biosimilar to have a lower incidence of immunogenicity than the reference product, so long as the lower incidence has no impact on effectiveness. Both the FDA and the EMA have published guidelines identifying the appropriate procedures for assessing ADAbs, including procedures, assays, definitions of one-assay and two-assay approaches, and cut-off points [20,25,39].

Pharmacovigilance: Monitoring biosimilar safety

For any approved drug, the goal of pharmacovigilance is to identify adverse events and understand, to the extent possible, their nature, frequency, and potential risk factors [46]. Doing so enables appropriate action to address adverse event(s). Despite its importance, pharmacovigilance is heterogeneous across countries. Recognizing the lag in pharmacovigilance in light of the growing uptake of biosimilars, an expert panel in Latin America was convened. The panel adopted six recommendations to facilitate the appropriate review, approval, and safe use of biosimilars across Latin America [47]. One of these called for the re-evaluation of products previously approved as “intended copy” biologic drugs according to regulations specific to biosimilars [47].

Pharmacovigilance encompasses all activities relating to the detection, assessment, and understanding of adverse events, including pharmacoepidemiologic studies, postmarketing surveillance, case reports, and possibly, preclinical data and events associated with other products in the same pharmacologic or biologic class [19,46]. A required element of pharmacovigilance is the ability to relate a reported event with a specific product (i.e., reference product or biosimilar) [18,19]. The importance of this has been a key consideration in the global discussion about naming biosimilars.

The pharmacovigilance plan may include efforts beyond routine postmarketing spontaneous reporting and is designed to enhance and expedite the biosimilar manufacturer’s acquisition of safety information [46]. Postmarketing safety monitoring may take into account any safety or effectiveness concerns associated with the reference product and its class [18,19]. Monitoring the safety profile of the biosimilar during development or through clinical use in other countries, if approved, may be included in the plan as well [19]. A basic pharmacovigilance plan developed by Calvo and Zuniga [48] is shown in Figure 3. Inclusion of one or more of the following elements may be recommended depending on safety signals observed during the comparability exercise [46].

- Expedited submission of specific serious adverse event reports
- More frequent submission of adverse event report summaries at prespecified intervals (e.g., quarterly rather than annually)
- Active surveillance to identify adverse events that may or may not be reported through passive surveillance—this process can be based on the biologic, setting, or event
- Additional postmarketing (phase 4), pharmacoepidemiologic studies (e.g., automated claims databases or other databases) using cohort, case-control, or other appropriate study designs
- Creation of registries (see above) or inclusion in existing registries
- Additional postmarketing and controlled clinical trials

As an example of postmarketing surveillance, the EMA has required the manufacturer of the biosimilar infliximab to maintain registries of patients with RA and inflammatory bowel diseases for the purpose of monitoring the risk of serious infections. Also, as is the case with most previously approved biologics, there is a

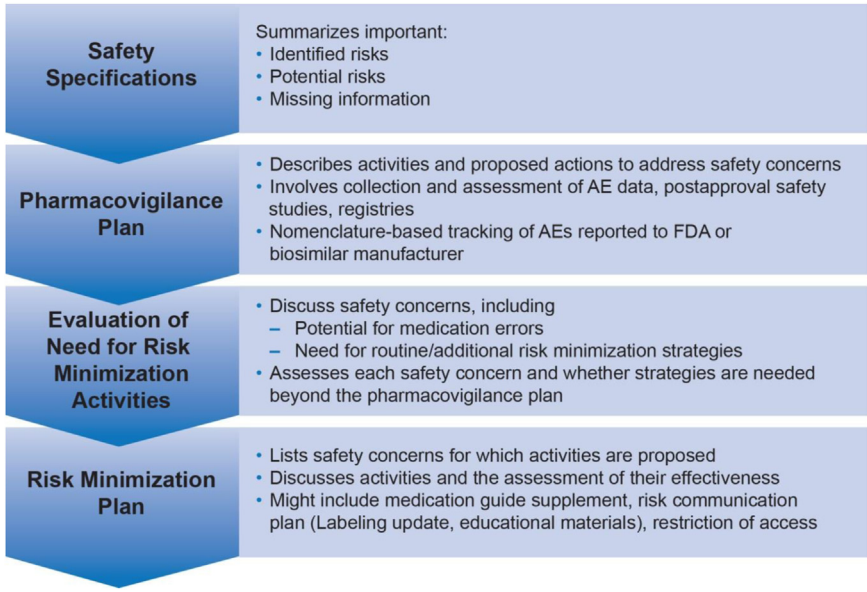

Fig. 3. Potential pharmacovigilance strategies for biosimilars [48].

requirement for planned and ongoing comparative studies and extension studies [5,6].

Postmarketing safety data often are used by regulatory agencies to make changes to the prescribing information for the biologic product. In the United States, the FDA can also require the establishment of a Risk Evaluation and Mitigation Strategy (REMS), which may include pharmacoepidemiologic studies or additional randomized clinical trials [49].

Interchangeability: Safety considerations

The FDA, but not the EMA, has the authority to approve a biosimilar as interchangeable with the reference product. To be approved by the FDA as interchangeable, a biosimilar must meet a higher standard. This higher standard requires that the biosimilar "can be expected to produce the same clinical result as the reference product in any given patient and, if the biologic product (biosimilar) is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biologic product and the reference product is not greater than the risk of using the reference product without such alternation or switch" [3,21]. The higher standard for interchangeability is intended to help insure patient safety.

The specific criteria to establish that a biosimilar is interchangeable with the reference product are currently under consideration by the FDA [38]. Crossover studies may be necessary, as was required for FDA approval of the subcutaneous route of administration for abatacept and tocilizumab, which were initially approved for intravenous administration [16,50–54].

Automatic substitutions: Implications for safety

While a physician can elect to switch a patient from a reference product to a biosimilar approved as interchangeable by regulators (and back again), automatic substitution enables a pharmacist to do the same, but without the approval or knowledge of the prescribing physician [3]. The safety implications of automatic substitution have added to the discussion about interchangeability. The Biologics Price Competition and Innovation Act (BPCIA) provided a legal definition of "interchangeable," and the FDA has established labeling requirements for biosimilars, which include a designation as to whether the biosimilar is or is not interchangeable with the reference product (although no established criteria for interchangeability currently exist) [19]. However, decisions regarding automatic substitution are left up to the states, which is similar to what occurred with generic small molecules. As of this writing, eight states in the United States have enacted legislation allowing substitution of biosimilars for reference products (Delaware, Florida, Indiana, Massachusetts, North Dakota, Oregon, Utah, and Virginia), with varying requirements for reporting to prescribers, pharmacists, and patients [55]. In Europe, this aspect is dealt with separately in each country. It also would be important to be better informed on variations of originator products in the future—awareness of this information has increased with the advent of biosimilars.

Nomenclature and safety

The naming of biosimilars focuses on the capability to differentiate one or more biosimilars from the reference product and each other, partly as a matter of public safety. The ability to track and identify the specific biologic product received by a patient is critical in the event of an adverse event [56].

The official naming of pharmaceutical and biologic products is determined on a national level. In the United States, there is not yet a guidance on naming conventions for biosimilars. The FDA is responsible for approving proprietary (i.e., branded) names of prescription products, while the United States Adopted Names Council (USAN) is responsible for selecting the names of nonproprietary (i.e., generic) prescription products [57]. The USAN is cosponsored by the US Pharmacopeia, The American Medical Association, and the American Pharmacists Association, with participation by the FDA. The nonproprietary names selected by the USAN are generally in agreement with those developed by the International Nonproprietary Names (INN) for Pharmaceutical Substances Expert Group of the World Health Organization (WHO).

The role of the WHO INN is to develop, establish, and promote international standards regarding biologic, pharmaceutical, and similar products, and specifically to select a single name of worldwide acceptability for each active substance that is to be marketed as a pharmaceutical [56,58]. In July 2014, the WHO INN

Expert Group recommended adoption of a two-part naming system for biosimilars [59]. The first part is the international nonproprietary name (INN), for which the selection process will remain unchanged. The second part is a biologic qualifier (BQ) consisting of four letters assigned at random. If adopted, the scheme will apply to all biologic substances to which INNs are assigned and is applicable retrospectively [59]. However, nomenclature for biosimilars is yet to be standardized.

Conclusions

Biologic agents, particularly monoclonal antibodies, are an important component of the treatment armamentarium for a range of inflammatory diseases. The clinical use of these biologic agents, and their biosimilars, may be associated with immune responses and other potential safety issues. Accordingly, the assessment of safety, particularly immunogenicity, is a key component throughout the stepwise biosimilar development process, as is the case with reference products. Several draft FDA guidances provide considerations for the design and conduct of safety assessments of biosimilars. These guidances include postmarketing safety assessments, which are intended to facilitate the timely management of safety concerns. Issues related to biosimilar nomenclature are being discussed globally, with the suggestion that the name of a biosimilar will be distinct from that of the reference product. Interchangeability and automatic substitution as well as cost issues also are being actively discussed. Finally, with regard to extrapolation of indications between diseases, it may be expected that an approved biosimilar showing similar efficacy and safety to a reference product in one or two indications, may also be similarly efficacious in other disease states for which the reference product is licensed. However, additional evidence may be reassuring for physicians. As biosimilar monoclonal antibodies are approved, these issues are likely to shape how these agents are used in clinical practice. In this respect, the experience procured in Norway, where the first EMA-approved mAb will be used nationwide, will be of particular interest.

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