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Clinical trial development for biosimilars

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ABSTRACT

Objectives: Discuss issues regarding clinical trial design for the development of biosimilars in the European Union and the United States, with special focus on monoclonal antibodies used in the treatment of inflammatory diseases.
Methods: A search of the Internet as well as PubMed was conducted through June 2014 for information related to the clinical development of biosimilars using the keywords biosimilar, rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and ankylosing spondylitis. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) websites were searched for biosimilar guidelines.
Results: The EMA began issuing draft guidelines for the development of biosimilars almost a decade ago and has approved numerous biosimilars. The US FDA has issued draft guidances providing stepwise considerations for the nonclinical and clinical development of biosimilars but has yet to approve a biosimilar under this pathway.
Conclusions: Clinical trials aim to resolve uncertainties that may remain following nonclinical development regarding the similarity of the proposed biosimilar with the reference product. Pharmacokinetic and pharmacodynamic studies form the backbone of early clinical development and serve to inform phase 3 clinical development. Factors to be considered in clinical development include study population, design, end points, sample size, duration, and analytical methods.

Introduction

The advent of biologic agents more than a decade ago has transformed the treatment of chronic inflammatory diseases (CIDs) such as rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), psoriasis (PsO), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), and ankylosing spondylitis (AS) [1]. These biologic agents include monoclonal antibodies or derivatives that target pro-inflammatory cytokines, most commonly tumor necrosis factor alpha (TNF-α) [2].

Despite the benefits of these biologic therapies for the treatment of these conditions, not all patients for whom their use is indicated receive them [3]. With the objective to increase access to biologic therapies, a pathway for the development of biosimilars, analogous to that created for the development of small-molecule generics, was created in the United States by passage of the Affordable Care Act (ACA), specifically the Biologics Price Competition and Innovation Act (BPCI) of 2009 (§351(k) pathway) [4].

Given the complexity of the molecular structure of biologics as well as their manufacture, it is not possible to manufacture identical molecules or "generics" for biologic agents. In response to BPCI, and with the differences between chemically synthesized small-molecule drugs and biologics in mind, the US FDA has released six draft guidances for the development of highly similar versions of biologics, also called biosimilars (Table 1) [5–10]. The FDA draft guidances had been preceded by guidelines released by the EMA in 2005. The EMA subsequently released numerous guidelines, many concerning monoclonal antibodies, and by the end of 2014 approved 19 biosimilars [11,12]. No biosimilars for a

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Table 1
FDA biosimilar regulatory guidances 2012–2014

Document	Purpose
Scientific considerations in demonstrating biosimilarity to a reference product	Outlines FDA "totality-of-the-evidence" approach toward demonstrating biosimilarity. The stepwise approach proceeds from structural and functional analysis, animal testing, and human PK/PD studies to clinical assessments of immunogenicity, safety, and efficacy [5]
Quality considerations in demonstrating biosimilarity to a reference protein product	Provides guidance on the types of analytical studies needed to determine whether a proposed biosimilar is highly similar to its reference product as part of a biosimilarity assessment [6]
Guidance for industry. Formal meetings between the FDA and biosimilar biologic products sponsors or applicants	Provides recommendations to industry on formal meetings with the FDA regarding biosimilar development [7]
Biosimilars: questions and answers regarding implementation of the BPCI Act of 2009	Provides answers to commonly asked questions from biosimilar developers and others regarding the agency's interpretation of the BPCI Act of 2009 (part of the ACA) [8]
Clinical pharmacology data to support a demonstration of biosimilarity to a reference product	Provides guidance on some of the overarching concepts related to clinical pharmacology testing (eg, PK and PD assessment) for biosimilar products, approaches for developing the appropriate clinical pharmacology database, and utility of modeling and simulation for designing clinical trials [9]
Guidance for industry. Reference product exclusivity for biological products filed under 351(a) of the PHS Act	Provides sponsors of biologic products with a summary of the information that will need to be submitted to FDA to help the agency determine the date of first licensure for a reference product [10]

chronic inflammatory disorder have been approved in the United States since the initial release of the FDA draft guidances in 2012. However, the FDA recently accepted applications from two manufacturers for the approval of biosimilars, which will be the first products reviewed under the 351(k) pathway, resulting from the BPCI Act [13,14]. As the patents of many other biologics, including those used to treat chronic inflammatory disorders, expire in the next few years, biosimilars for biologics such as abatacept, adalimumab, infliximab, rituximab, and tocilizumab are and will be in development [2,15].

Both the FDA draft guidances and the EMA guidelines for biosimilar development recommend a scientifically rigorous stepwise process that is different from that for generic small-molecule drugs. This article highlights some of the key recommendations included in the FDA guidances for biosimilar development, focusing on those related to clinical development in humans.

FDA definition of a biosimilar

The FDA describes biosimilars in the following way: "The biologic product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there are no clinically meaningful differences between the biologic product and the reference product in terms of safety, purity, and potency of the product" [5]. This definition makes it clear that biosimilars are not exact copies of the reference product, and that any differences in purity and potency between the biosimilar and reference product must not be clinically meaningful.

Why are biosimilars different from the reference product?

As highly complex proteins, biologics and biosimilars require a more complex manufacturing process than small-molecule drugs [2]. Because there is a strong relationship between the manufacturing process of a biologic and the characteristics of the final product [16], manufacturing processes typically remain proprietary information [2,16–18]. Therefore, with today's technology, producing an exact copy of a reference product is not possible. Even small alterations in source materials invariably lead to changes in the molecular structure of the biologic molecule, and possibly in its biologic effects and breakdown products [2].

During production of biologics including biosimilars, it can be difficult to avoid batch-to-batch variability and changes in the identity, strength, and purity of the biologic product over time, which is associated with "process drift." Examples of changes include alterations in the product's isoforms, three-dimensional protein structure, quantity of acid–base variants, and glycosylation profile. Changes such as these, which often are due to variability in source materials, cell line used, extraction and purification processes, and scale changes, may result in alterations to clinical efficacy or safety [16,19]. Therefore, when such a change occurs, the manufacturer of the biologic product is required to conduct a complex and multicomponent comparability exercise to demonstrate that the change does not adversely affect the identity, purity, or potency of the currently approved biologic product [6]. The comparability exercise, described in the International Conference on Harmonization (ICH) Q5E guidance, consists of analytical testing, biologic assays, and, in some cases, nonclinical and clinical studies [20]. In comparison, EMA and FDA requirements for biosimilars follow the same principles but are more extensive and require nonclinical and clinical studies. This difference is due to the fact that comparability for a reference product is assessed within the same manufacturer and based on known process changes, whereas biosimilar development is a process that has to be devised de novo based on the fact that there are now different manufacturers involved [6,21].

FDA draft guidances on clinical development of biosimilars

As with a novel biologic, the development of a biosimilar follows a scientifically rigorous, stepwise process. However, unlike a novel biologic, the biosimilar also follows a totality-of-the-evidence approach that emphasizes physicochemical, biologic, and preclinical studies to establish biosimilarity, with clinical development focused on confirming and resolving any remaining uncertainties regarding biosimilarity (Fig. 1) [5,9,21]. Because experience with the reference product serves as the base, the primary goal of biosimilar development is to demonstrate that the purity, potency, and safety of the biosimilar are similar to the reference product rather than independently establishing the efficacy and safety of the biosimilar [5]. However, one or more clinical studies are required to demonstrate the safety of the biosimilar [5].

To meet the FDA requirements, clinical development of the biosimilar begins with studies to demonstrate comparable pharmacokinetics (PK) and pharmacodynamics (PD) with the reference product in a relevant population [9]. Also included in early clinical development are investigations that focus on safety, including immunogenicity (see "Biosimilar Safety Factors in Clinical Practice"

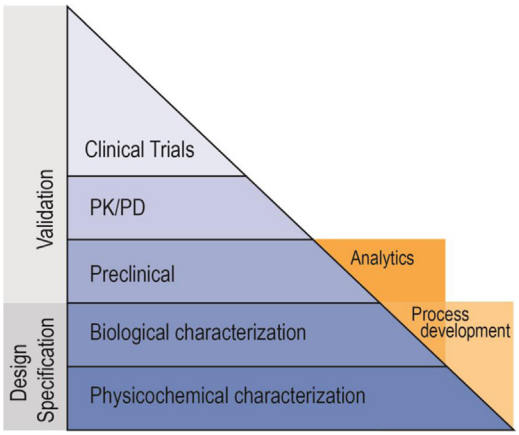

Fig. 1. Relative data requirements for novel biologics and biosimilars. The data requirements to support regulatory approval of a novel biologic product involve greater emphasis on phase 1, 2, and 3 clinical development, whereas development of a biosimilar involves greater emphasis on nonclinical (physicochemical, biologic, and animal) development. PD = pharmacodynamic; PK = pharmacokinetic [21].

in this issue). Once PK, PD, and immunogenicity similarity to the reference product has been demonstrated, at least one phase 3 clinical comparability trial is conducted to confirm similar efficacy and safety in a sensitive population [21].

Considerations for early clinical studies

PK and PD studies that demonstrate similarity in humans between the biosimilar and the reference product may provide a scientific basis for a selective and targeted approach to further clinical testing [5]. PK studies determine what the body does to the biologic, while PD studies determine what the biologic does to the body [22]. A range of 80–125% generally is used to demonstrate equivalence at the 90% confidence level for PK/PD evaluations [23,24]. The PK study assesses exposure to all active components of the reference product as measured by dose (drug input to the body) and various measures of single or integrated drug concentrations in plasma and other biologic fluid, for example, peak concentration (C_{max}), lowest concentration measured following dosing (C_{min}), concentration prior to the next dose during multiple dosing ($C_{trough\ ss}$), and area under the plasma/blood concentration–time curve (AUC) [9]. PD markers assess response to the reference product [9]. For selecting PD markers, it is important to consider: (1) time of onset of the PD marker relative to dosing, (2) dynamic range of the PD marker over the exposure range to the reference product, (3) sensitivity of the PD marker to differences between the biosimilar and the reference product, (4) relevance of the PD marker to the mechanism of action of the reference product, and (5) relationship between changes in the PD marker and clinical outcomes [9].

For PK as well as PD evaluations, assessing measures known to be clinically relevant to effectiveness can provide strong support to the demonstration of biosimilarity. For PK, a common measure is exposure (eg, serum concentration over time) [5]. For PD, examples of measures include the American College of Rheumatology 20% (ACR 20) response rate and Disease Activity Score 28 (DAS28) in RA, the Crohn's Disease Activity Index, and the Ankylosing Spondylitis Disease Activity Score (ASAS or ASDAS) [25–27]. Although PD end points or assays that are sensitive and clinically important are established for many inflammatory disorders, no direct PD measurements can be attributed to antitumor necrosis factor biologics in patients [28]. When PD end points are not closely related to clinical outcome, use of multiple complementary PD assays may be the most useful. Because the PD assay is highly dependent on the pharmacologic activity of the biosimilar, the approach for assay validation and the characteristics of the assay performance may differ depending on the specific PD assay. Demonstration of specificity, reliability, and robustness remain as guiding principles for choosing PD assays [9]. Discussion with regulatory agencies may be appropriate where end points are not well established.

Clinical trials evaluating PK and PD are generally designed based on the selected population and related factors, as well as what is known regarding the intra- and intersubject variability of human PK and PD for the reference product [5]. Clinical pharmacology studies should be conducted in the subject or patient demographic group most likely to provide a sensitive measure of differences between the biosimilar and reference product. The total number of subjects should provide adequate power for similarity assessment [9]. For many drugs, human PK and PD studies are conducted in healthy volunteers if the product can be administered safely to this population [9]. For biologics, however, there are some key considerations regarding the use of healthy volunteers. First, healthy subjects may have a greater immunogenic response than a population with disease (depending on whether the background standard of care in the population is immunosuppressive and other population factors) [9,29]. Second, healthy subjects are not appropriate if the disease relevant to the indication, or its treatment, is known to alter the PK of the reference product [9,30]. Differences in PK related to sex, race, renal function, or hepatic function also may require special consideration.

Clinical trials of biosimilars used for inflammatory disorders usually are carried out with a parallel design rather than a crossover design. In a parallel design, subjects are randomized to one of the two (or more) treatment groups. While the treatments differ between groups in a parallel design, all subjects are otherwise treated as similarly as possible. In a crossover study, a subject receives one treatment during the first study period and a different treatment during the second study period, with a washout phase between the two periods to allow the body to clear the first treatment [5,9,31,32]. Because the elimination half-life of biologics used for inflammatory disorders is often a week or longer, the washout phase may be weeks or months, making a crossover design impractical [9]. Furthermore, a crossover design may not be appropriate if patients do not have stable disease [32]. In addition, the washout period in a crossover design often leads to flare of the inflammatory disease, which can result in an enhanced placebo response as the flare often subsides on its own.

The dose and route of administration should be the same as for the reference product [33]. If the reference product can be administered in several doses or via more than one route, the dose and route of administration to be tested in clinical trials are those determined to be the most sensitive to detect differences in PK and PD between the biosimilar and reference product [5]. Therefore, the dose chosen is the one for which the reference product is indicated and that is on the steepest part of the dose–response curve [5]. Modeling and simulation tools can be useful in the selection of an optimally informative dose or doses for evaluating PD similarity [9].

Considerations for phase 3 clinical comparability trials

Phase 3 clinical comparability trials are intended to resolve uncertainties that remain regarding the efficacy and safety of the biosimilar relative to the reference product following completion of physicochemical, biologic, and preclinical investigations, as well as PK, PD, and immunogenicity investigations in humans [5]. In addition, a history of safety concerns with the reference product may warrant more extensive phase 3 clinical investigation of the

biosimilar, whereas a long and relatively safe marketing history may warrant a selective and targeted approach [5].

For biosimilar development, phase 3 clinical equivalency trials should demonstrate that the proposed biosimilar has neither decreased nor increased activity relative to the reference product [5]. That is, the goal is to demonstrate that any difference in efficacy or safety between the biosimilar and reference product is less than a prespecified margin of "clinical equivalence" [34]. Such an equivalence margin is the crux of the trial and could be based on the historical differences observed in the treatment effect for the reference product versus placebo [33,35]. Trial designs for biosimilar development are not unlike designs for any other biologic product with similar considerations of patient population, sample size, end points, and study duration. Clinical development of a biosimilar also provides a stringent head-to-head comparison with the reference product.

Study designs

Superiority trials, which are typically used to demonstrate superiority of one treatment over another (such as placebo), are not appropriate for biosimilar development because demonstrating superiority is not a goal. Instead, nonsuperiority trials are more useful when evaluating biosimilars. Nonsuperiority trials can be categorized as equivalence or noninferiority designs [36]. Both design options are included in the 2012 FDA scientific draft guidance [5]. In practice, however, an equivalence design generally is used because demonstrating that the biosimilar is equivalent to the reference product is the goal.

In an equivalence trial, which uses a two-sided test based on a prespecified range, the null hypothesis is that the biosimilar is either (1) inferior to the reference product or (2) superior to the reference product based on a prespecified equivalence margin [5]. The equivalence margins are chosen to enable detection of clinically meaningful differences in effectiveness between the biosimilar and reference product at the 95% confidence interval [35]. The upper (superiority) and the lower (inferiority) bounds of the equivalence margin generally will be the same [5]. The goal in an equivalence design is to reject the null hypothesis of nonequivalence and accept the alternative hypothesis that the two treatments (in this case, the biosimilar and the reference product) are equivalent (ie, the differences between the two are not clinically and statistically meaningful) [34]. This is done by determining if the difference in the primary end point between the reference product and biosimilar is within the equivalence margin at the 90% or 95% confidence interval. In Figure 2, the two treatments are

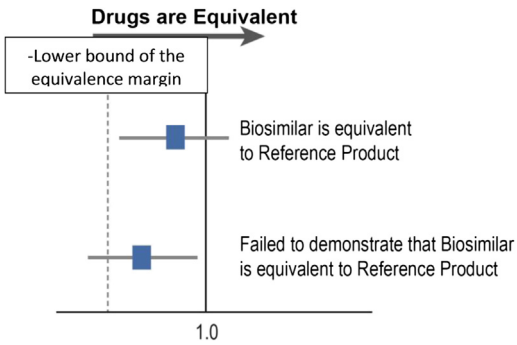

Fig. 2. Trial design: equivalence. In an equivalence trial, if the lower boundary of the 95% CI of the difference between the two products (biosimilar vs reference product) does not cross the null boundary (equivalence margin), then the biosimilar and reference product are equivalent. If the lower boundary of the 95% CI crosses the null boundary, equivalence between the two products cannot be concluded. CI = confidence interval [34]. Adapted with permission from Springer Science+Business Media: Dranitsaris et al. [34]

equivalent because the lower boundary of the 95% confidence interval is greater than the lower equivalence margin [34].

As an example, the phase 3 clinical comparability trial Program evaLuating the Autoimmune Disease iNvEstigational Drug CT-P13 in RA Patients (PLANETRA) compared a biosimilar with reference infliximab in patients with active RA and an inadequate response to methotrexate. The prespecified equivalence margin was selected to be 15%, or 50% of the treatment effect observed in clinical trials with the reference product. At week 30, the ACR 20 response was 60.9% in patients treated with the biosimilar and 58.6% with the reference product [25]. As the 2.3% difference between the two biologics and 95% CI of the difference (−6% and 10%) was within the prespecified margin of 15%, the biosimilar was considered to have efficacy equivalent to the reference product in this patient population [25].

A one-sided noninferiority design may be advantageous in some situations, as this design allows for a smaller sample size than an equivalence design [5]. This design may be appropriate if it is well established that the reference product is used at or near the maximal level of clinical effect. Because one of the goals of biosimilar development is to establish that the biosimilar does not confer a higher safety or immunogenicity risk than the reference product, a noninferiority design may be adequate for the evaluation of immunogenicity or other safety outcomes, provided that lower immunogenic or other safety events would not have efficacy implications [5]. Using a one-sided noninferiority design, demonstration that one product is not inferior to another does not mean the two products are equivalent [37], and, thus, it is not generally appropriate for complex biologics used for the treatment of inflammatory diseases.

Determination of sample size

The sample size and duration of the phase 3 clinical and efficacy trials should allow (1) sufficient exposure to the biosimilar and reference product; (2) detection of relevant safety signals (including immunogenicity), except for rare events or those that require prolonged exposure; and (3) detection of clinically meaningful differences in effectiveness and safety between the biosimilar and reference product. Sample size needs to be carefully considered, as it is one of the most important determinants of the power of a study (likelihood that if a difference between treatments exists the trial will demonstrate this with statistical significance). The sample size may be influenced by the specific treatment effect(s), the effect size of the reference product, and the equivalence margin because the sample size increases as the equivalence margin narrows [5,36]. Determination of the sample size in an equivalence trial is similar to that in a superiority design except that an equivalence trial must consider the equivalence margin in the determination [38]. One-sided noninferiority designs generally require a smaller sample size than trials using a two-sided design [38].

Determination of study duration

The duration of the phase 3 trial(s) should reflect the clinical reality of the disease in which the biosimilar is being investigated. Experience with the reference product and other agents within the class may be useful as a guide [5]. Because most rheumatologic conditions are chronic in nature with periods of exacerbations and remissions, the phase 3 clinical trial should be long enough for the biosimilar to exert its advantageous as well as deleterious effects [36]. A possible drawback of trials of long duration is longitudinal bias, as this may affect the efficacy comparison. Longitudinal bias can result from interference of patient/physician behaviors, comedications, and selective dropouts [36]. This seems less likely for the development of a biosimilar than with a clinical trial, comparing a new treatment with a standard therapy or placebo. It is also

important to be aware of the fact that many clinically important adverse events occur at a relatively low frequency, and the probability of them occurring during the time frame of the clinical trial is low [36]. For this reason, pharmacovigilance measures are critical and required for long-term assessment of safety.

Selection of end points

When comparing a biosimilar with a reference product, it is important to select end points that are both relevant to the disease state in question and sensitive enough to detect clinically relevant differences in efficacy and safety, if any, between the biosimilar and its reference product [5]. End points generally should be one or more of those used during clinical trials of the reference product; if not, the choice should be scientifically justified [5]. For many inflammatory diseases, these end points usually are consistent with the Outcome Measures in Rheumatology (OMERACT) framework (www.omeract.org).

Two types of efficacy end points may be chosen. Clinical end points are those that directly affect the patient, while surrogate end points or markers reflect a situation that is associated with a real end point but does not yet affect the patient [36]. In rheumatology, there are no currently accepted surrogate markers because many biomarkers are confounded by factors unrelated to the immune disorder [39].

Use of adaptive design and interim analysis

Although the biosimilar development process is designed to enable a selective and targeted approach to clinical development, the time and resources required for clinical development remain considerable. Consequently, there is interest in additional strategies to further refine the clinical development of biosimilars. One approach may be to use an adaptive design clinical trial, which recently has been used in phase 3 studies of an innovator biologic for the treatment of UC [40,41]. The adaptive design includes a prospectively planned opportunity for modification of one or more specified aspects of the study design or hypotheses based on analysis of data (usually interim data) [42]. Analyses of the interim data can be performed in a fully blinded manner or in an unblinded manner and can occur with or without formal statistical hypothesis testing. When unblinded, safeguards for study integrity must be assured [42].

Adaptive study design allows a broad range of protocol modifications, eg, eligibility criteria, sample size, treatment regimen, and primary and secondary end points [42]. Benefits of adaptive design trials include streamlining clinical development and minimization of costs. Adaptive design trials also are potentially more informative [42].

Adaptive design trials, however, have the potential for introduction of bias and the possibility for erroneous conclusions, although modifications may be made to adequately account for the changes in analysis [42]. In the case of either a robust demonstration of efficacy or, conversely, no observed treatment effect, methods such as the O'Brien–Fleming boundary can be used to facilitate early study termination [42]. To date, no adaptive design trial has been used in the clinical development of biosimilars.

Intention-to-treat and per-protocol analyses

Intention-to-treat (ITT) and per-protocol (PP) analyses are the two common approaches to data analysis for clinical trials. The ITT approach maintains the integrity of the randomization because it includes all the subjects who were randomized whether or not they received the assigned treatment (and those who withdrew from the study for any reason including protocol violations). The PP approach includes only those subjects who received the assigned treatment and followed the protocol. Consequently, in a superiority trial, the PP analysis provides an optimized comparison of treatment groups, while the ITT analysis provides a conservative comparison. In contrast, ITT analysis tends to increase the likelihood of a positive result in equivalence or noninferiority trials. In these trials, a PP analysis would be the more conservative and, thus, preferred approach, while ITT analysis can be used as a secondary analysis [34,37].

Data extrapolation

As part of their guidances for biosimilar development, the FDA has provided recommendations regarding extrapolation of clinical data across indications. Provided that similarity of the biosimilar has been established by meeting the FDA requirements for licensure, the potential exists for the biosimilar to be licensed for one or more additional indications for which the reference product is licensed. To do this, scientific justification must be provided for extrapolating clinical data for each condition [5]. A key consideration for extrapolation is the selection of a sensitive population to be studied in the phase 3 clinical trial, that is, the population in which clinically meaningful differences in safety (including immunogenicity) and effectiveness between the biosimilar and reference product are most likely to be detected [5].

Although the FDA guidance generally is consistent with those issued by the EMA and the World Health Organization (WHO) [31,43], there are differing viewpoints among regulatory agencies and healthcare professionals. This subject will be discussed in an upcoming supplement.

Table 2
Key considerations in evaluating phase 3 clinical studies of biosimilars

Comparability	An equivalence design at the 90% or 95% confidence interval is used (generally preferred to a noninferiority design) An equivalence design establishes that the biosimilar is neither superior nor inferior to the reference product [5]
Patient population	Should be clinically relevant Does the study use the most sensitive patient population, that is, the population in which clinically meaningful differences in safety and effectiveness between the biosimilar and reference product are most likely to be detected [5]?
Power/sample size	Study is sufficiently powered to detect potential differences between biosimilar and reference product [5,36]
Dose	The dose and route are consistent with the reference product [5]
End points	End points are relevant to the disease state and sensitive enough to detect clinically relevant differences in efficacy and safety, if any, between the biosimilar and reference product [5]
Study duration	The duration of the study was appropriate to detect clinical effects [5,36]
Statistical analysis	A per-protocol analysis includes only patients who followed the protocol, whereas an intention-to-treat analysis includes all randomized patients If the study used an equivalence design, a per-protocol analysis was used [34,37]
Efficacy	Are efficacy measures within the prespecified acceptable margin of equivalence [5]?
Safety	Are the incidence and types of AEs comparable between biosimilar and reference product [5]?

Lessons learned

Although biosimilar development provides the opportunity for a selective and targeted clinical program to address unresolved issues following completion of preclinical testing, a phase 3 clinical comparability trial, in addition to early clinical testing, is an essential part of the process. For example, during clinical development of one biosimilar, an increase in anti-human growth hormone antibody incidence was only detected during the conduct of the phase 3 trial. This observation was made despite a demonstration of similarity with physicochemical, biologic, and preclinical studies using state-of-the-art methods. Implementation of a sensitive, process-specific assay identified the source of the problem, with its resolution confirmed through additional phase 3 clinical testing [44].

Summary and conclusions

Biologics play an important role in the treatment of inflammatory conditions such as RA, JIA, PsO, PsA, CD, UC, and AS. In Europe, the EMA has released numerous guidelines to facilitate clinical trial development, many concerning monoclonal antibodies, and has approved 19 biosimilars to date. In the United States, in an attempt to increase patient access to biologic products, a pathway was created by passage of the BPCI Act of 2009 and the release of draft guidances by the FDA in 2012–2014 to facilitate this pathway. The FDA identifies a targeted but key role for clinical investigations to resolve uncertainties remaining following completion of analytical and preclinical investigations. The design and conduct of clinical trials of biosimilars follow principles similar to those used for clinical trials of most drugs and biologics, although establishing superiority to the reference product is not a goal. Study design elements must be determined carefully as they are critical determinants of detecting clinically meaningful differences in safety and effectiveness between the biosimilar and the reference product (Table 2).

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