The development of biosimilar products is an area of growing interest in the global medical community. This article will review current regulatory recommendations, as well as discuss key considerations for the early clinical phases of biosimilar development.

Considerations in the early development of biosimilar products

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The widespread use and patent expiration of many biologics have led to global interest in development of biosimilar products. Because the manufacture of biologics, including biosimilars, is a complex process involving living systems, the development of a biosimilar is more rigorous than the development of a generic small molecule drug. Several regulatory agencies have established or are proposing guidelines that recommend a stepwise process to ensure the efficacy and safety of a biosimilar are highly similar to the reference product. This article also explores the early clinical phase of biosimilar development, which is particularly important to resolving any uncertainties that might remain following in vitro and in vivo evaluations and to enable a selective and targeted approach to Phase III efficacy and safety investigation.

Introduction

The introduction of targeted biologics has been a major advance for the treatment of diseases and conditions such as cancer (active treatment and supportive care), rheumatoid arthritis, diabetes mellitus and other autoimmune disorders. The rapid emergence of biologics has led to widespread and global use. In 2012, five of the top ten global prescription products were biologics [1]. Sales of biosimilars, accounting for 0.4% of the global biologics market, are increasing [2]. In Europe, by volume, biosimilars make up 12% of the epoetin alfa market, 7% of the growth hormone market and 18% of the filgrastim market [3].

The patents of some key biologics recently expired, and many more are going off-patent in the coming years. Coupled with current global socioeconomic, ongoing concern regarding patient access to biologics and further technologic innovations, a shift in pharmaceutical product development is occurring, giving rise to the development of biosimilars [1,4]. Whereas the active ingredient of a generic drug product is chemically identical to a brand name drug, a biosimilar as a biological product cannot be identical to its reference product. The biosimilar product must be highly similar to an existing biologic branded product with no clinically meaningful differences.

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Because the molecules are unlikely to be chemically identical, a biosimilar cannot be considered a generic form of an existing biological product. Definitions of a biosimilar by regulatory agencies, as well as other related terms discussed in this article, are provided in the Glossary [5–7].

In 2005, the European Medicines Agency (EMA) became the first drug regulatory body to develop, approve and publish guidelines for the development of biosimilars [8]. The EMA approved the first biosimilar product (somatropin) in April 2006. In 2009, WHO released its own guidelines for biosimilar development, which were based on the EMA principles [9]. The FDA released a series of draft guidances from 2012 to 2013 following authorization under the Biologics Price Competition and Innovation Act subsection of the Patient Protection and Affordable Care Act of 2009 [10]. Several countries (e.g. Australia, Canada, China, India, Japan, Korea, Mexico, among others) have developed or are developing their own pathways for biosimilar approval based in part on the regulatory paradigm for biosimilar products outlined by the EMA. As of December 2014, the EMA has approved more than 20 biosimilar products, including the first biosimilar monoclonal antibody [11].

Although in draft form, the FDA guidances provide comprehensive recommendations to sponsors. Until the FDA validates this guidance by approving the first biosimilar via the 351(k) pathway, uncertainties regarding the standards required for biosimilarity could remain. Unlike the EMA, the FDA has the statutory authority to approve biosimilar products as interchangeable. The higher standards required to qualify as interchangeable have not yet been issued by the FDA. In general, the EMA and FDA biosimilar guidelines are aligned, considering the differing level of maturity of the biosimilar pathways put into place by different legislative bodies worldwide. In general, regulatory guidelines make it evident that development of a biosimilar requires extensive investigation to demonstrate that the proposed biosimilar is highly similar to the reference biological product.

The stepwise development of a biosimilar involves an extensive side-by-side comparison of quality data between the biosimilar and its reference biological product followed by a transition from nonclinical laboratory and animal testing to early clinical development (Phase I) and finally Phase III development in humans to resolve any remaining uncertainty that the biosimilar might not be similar to the reference product. (While there are variations in how they are defined, for the purposes of this article, preclinical studies refer to studies conducted in animals, whereas nonclinical studies include all studies not conducted in humans. Therefore, nonclinical studies include preclinical studies, as well as physicochemical and biological studies.) This article explores the regulatory guidelines for early clinical development of a biosimilar product, because these guidelines shape the clinical development program, and defines key considerations in the early clinical development program. Additional considerations in the early clinical development of a biosimilar also are explored, with suggestions to resolve decisions commonly encountered in the early clinical development of a biosimilar.

**Overarching goal of the early clinical development program of a biosimilar product**

An overarching goal of the biosimilar development program for its sponsor is to receive the same approved labeling as the reference product without having to repeat clinical studies in every licensed indication. This requires evidence gained through the comprehensive development process of a biosimilar. Although there is no one path to develop a given biosimilar product, regulatory agencies have put guidelines in place that recommend an extensive comparability exercise consisting of a rigorous, scientific-focused, stepwise development process, with each step building on previous ones (Fig. 1) [6,7]. Clinical development consists of an early phase (typically considered Phase I) and a late phase (Phase III). Early clinical development includes evaluations of pharmacokinetics (PK), pharmacodynamics (PD) and safety/immunogenicity in humans.

**Regulatory guidelines regarding biosimilars: European Union and USA**

The legal pathway for the regulatory approval of biosimilars was first adopted in European Union (EU) legislation in 2004 and came into effect in 2005. Based on this, the EMA established the regulatory pathway in 2005 with the release of guideline CHMP/437/04 [8]. This guideline provided the regulatory framework as a resource for sponsors that ‘may choose to develop a new biological medicinal product claimed to be ‘similar’ to a reference medicinal product, which has been granted a marketing authorization in the [European] Community’ [8]. In addition to the 2005 guideline, which is undergoing revision, the EMA has released several product-class-specific guidelines (e.g. for low-molecular-weight heparins and monoclonal antibodies).

**EMA and FDA biosimilar guidelines**

Despite sharing many fundamental points, there are differences between the EMA and FDA biosimilar guidelines that could be important considerations when undertaking the biosimilar development process (Table 1). The FDA can approve both a biosimilar and an interchangeable biosimilar [7]. Individual
states, however, can pass legislation to regulate interchangeability. Although biosimilars are approved by the EMA, which issues a Pan EU Marketing Authorisation, the EMA is silent on interchangeability status for this reason and each individual national member state must determine their policy with respect to interchangeability. For the FDA to approve a biosimilar as interchangeable with the reference product, the sponsor must demonstrate that ‘the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product [biosimilar] and the reference product is not greater than the risk of using the reference product without such alternation or switch’ [12,13].

Another, more-data-driven difference is that EMA guidelines emphasize in vitro nonclinical assessment rather than in vivo toxicology studies, which is in keeping with EU Directive 2010/63/EU regarding the protection of animals used for scientific purposes [14]. The FDA has the ability to waive requirements for in vivo toxicology assessment, but typically does not do so in the absence of sufficient clinical data.

Among the commonalities of the EMA and FDA guidelines for biosimilar development is to approve biological products for marketing that have established similarity between the proposed biosimilar and reference biological product through extensive comparative assessments. This goal differs from that of generic small molecules, where establishing bioequivalence to the reference product through an exercise comparing bioavailability is sufficient [6]. In establishing similarity between the proposed biosimilar and the reference biological product, it is important to show that the previously demonstrated safety and efficacy of the reference biological product also applies to the proposed biosimilar [6,7]. In general, at least one Phase III clinical efficacy and safety trial is required to demonstrate similarity relative to the reference product. However, establishing efficacy and safety of the proposed biosimilar are not objectives of the biosimilar development process [6,7]. In limited circumstances, such as for structurally more simple biological medicinal products, a clinical efficacy study might not be necessary if similarity of physicochemical characteristics and biological activity or potency of the proposed biosimilar and the reference product can be convincingly shown and similar efficacy and safety can clearly be deduced from these data and comparative PK data. In vitro and/or clinical PD data might be needed for support [6]. Although not described by the EMA or FDA, examples of structurally less complex biosimilars might be insulin and heparin.

To establish similarity between the proposed biosimilar and reference biological product, the EMA and FDA require that the stepwise comparability assessment be scientifically rigorous. The type and amount of analyses and testing that will be sufficient to demonstrate similarity will be determined on a product-specific basis [7]. Each step of the comparability assessment is intended to build on the preceding steps, with each step serving to resolve as much remaining uncertainty as possible regarding similarity between the proposed biosimilar and reference biological product. Consequently, physicochemical and biological characterizations serve as the beginning and foundation of the stepwise approach. Together with the subsequent preclinical studies (in vitro and, if needed, in vivo), these preceding steps collectively serve to inform the nature and extent of the clinical development program [6,7]. Thus, more comprehensive and robust physicochemical, biological and preclinical investigations provide scientific justification for a selective and targeted approach to clinical testing [7]. A targeted approach is further supported by resolving the clinical importance of any differences found between the proposed biosimilar and reference biological product early in the stepwise development process.

In the EU and the USA, the reference product is legally defined as having been approved or licensed in the respective region using a full complement of safety, quality and efficacy data; thus, a biosimilar product cannot serve as a reference product for another
TABLE 1
General guidelines for biosimilar development

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Effective date</th>
<th>Purpose or focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Medicines Agency Guidelines on Similar Biological Medicinal Products</td>
<td>October 2005 (under revision)</td>
<td>To introduce the concept of similar biological medicinal products; to outline the basic principles to be applied; and to provide applicants with a ‘user guide’, showing where to find relevant scientific information in the various Committee for Medicinal Products for Human Use (CHMP) guidelines, to substantiate the claim of similarity [8]</td>
</tr>
<tr>
<td>Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues</td>
<td>June 2006 (under revision)</td>
<td>To outline the nonclinical and clinical requirements for a biological medicinal product claiming to be similar to another one already marketed. The nonclinical section addresses the pharmacological assessment. The clinical section addresses the requirements for pharmacokinetics (PK), pharmacodynamics (PD), and efficacy studies. The section on clinical safety and pharmacovigilance addresses clinical safety studies as well as the risk management plan with special emphasis on studying the immunogenicity of the similar biological medicinal product [34]</td>
</tr>
<tr>
<td>Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substances: Quality Issues</td>
<td>June 2006 (under revision)</td>
<td>To outline the quality requirements for a biological medicinal product claiming to be similar to another one already marketed. The guideline addresses the requirements regarding manufacturing processes, the comparability exercise for quality, considering the choice of reference product, analytical methods, physicochemical characterization, biological activity, purity and specifications of the similar biological medicinal product [35]</td>
</tr>
<tr>
<td>Questions and Answers on Biosimilar Medicines (Similar Biological Medicinal Products)</td>
<td>September 2012</td>
<td>Not stated</td>
</tr>
<tr>
<td>FDA Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product</td>
<td>Draft</td>
<td>To assist sponsors in demonstrating that a proposed therapeutic protein product is biosimilar to a reference product for purposes of the submission of a marketing application under section 351(k) of the Public Health Service (PHS) Act [7]</td>
</tr>
<tr>
<td>Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity to a Reference Product</td>
<td>Draft</td>
<td>To provide recommendations to applicants on the scientific and technical information of the chemistry, manufacturing and controls (CMC) section of a marketing application for a proposed biosimilar product submitted under section 351(k) of the PHS Act [10]</td>
</tr>
<tr>
<td>Guidance for Industry: Formal Meetings Between the FDA and Biosimilar Biological Products Sponsors Draft for Applicants</td>
<td>Draft</td>
<td>To provide recommendations to industry on formal meetings between the FDA and biosimilar biological product sponsors or applicants [36]</td>
</tr>
<tr>
<td>Guidance for Industry: Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009</td>
<td>Draft</td>
<td>To provide answers to common questions from sponsors interested in developing proposed biosimilar products, biologics license application holders and other interested parties regarding the FDA interpretation of the Biologics Price Competition and Innovation Act of 2009 [37]</td>
</tr>
<tr>
<td>Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product</td>
<td>Draft</td>
<td>To assist sponsors with the design and use of pharmacology studies to support a decision that a proposed therapeutic biological product is biosimilar to its reference product [38]</td>
</tr>
<tr>
<td>WHO Guidelines for Evaluation of Similar Biotherapeutic Products (SBPs)</td>
<td>October 2009</td>
<td>To provide globally acceptable principles for licensing biotherapeutic products that are claimed to be similar to biotherapeutic products of assured quality, safety and efficacy that have been licensed based on a full licensing dossier [9]</td>
</tr>
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proposed biosimilar. To facilitate global development, however, the EU and the USA allow bridging to the respective EU or USA reference product (or a reference product approved or licensed in another region with standards compatible with the International Conference on Harmonization) via comparative analytical and PK data to allow selection of a single comparator to be used in the single global Phase III study and any preceding in vivo toxicology studies [6,7]. Comparison to a reference biological product approved or licensed by another regulatory agency with similar scientific and regulatory standards (i.e. one that adheres to standards adopted by the International Conference on Harmonization) is required. Justification for the use of a product approved by another regulatory agency must be made and supported by data from analytical and/or comparative PK studies [6]. Prior to using a product approved by another regulatory agency as a comparator, it might be advisable for the sponsor to consult with the regulatory agency and provide the scientific justification for using the selected product.

**General considerations for clinical development of a biosimilar**

Comparative assessments of PK and PD occur in early clinical development, whereas evaluations related to unresolved efficacy, safety and immunogenicity issues mainly occur in Phase III...
clinical development of a biosimilar (Fig. 1) [7,15]. Following regulatory approval of a biosimilar (and biologics in general), postmarketing surveillance, particularly to identify rare adverse events, is an important step [7,15]. Clinical development must include studies (including PK, PD and assessment of immunogenicity) sufficient to demonstrate safety, purity and potency of the proposed biosimilar in appropriate conditions for which the reference product is licensed and for which licensure is sought for the biosimilar [7]. In conducting clinical studies, endpoints and study populations are selected that will be clinically relevant and sensitive in detecting clinically meaningful differences [7].

**Strategic design of early clinical development of a proposed biosimilar**

A strategically designed early clinical development program could allow a selective and targeted approach to the Phase III clinical trial(s) of efficacy, safety and immunogenicity. Establishing the PK similarity to a licensed or approved reference product in a sensitive and homogeneous population is the first step of the clinical program of a proposed biosimilar. When clinically relevant PD markers are available, comparative assessment of the PD effects between the proposed biosimilar and a reference product can add information for the biosimilarity determination and lead to a more targeted approach to the Phase III clinical program. Evaluation of immune response in the early clinical stage can provide initial immunogenicity data for the proposed biosimilar. It also can facilitate the use of appropriate assays and an optimal study design for the comparative immunogenicity assessment in the Phase III trial.

**Approach to resolving remaining uncertainties**

Another strategic decision relates to the extent of the uncertainties regarding similarity that remain following the nonclinical phase of development. In considering which of these remaining uncertainties to address, the key question for the sponsor of the biosimilar, as well as the regulatory agency, is: how similar is similar enough [16]? If no or minimal differences between the proposed biosimilar and reference product are observed during the physicochemical and in vivo nonclinical investigations, the clinical investigations can follow a targeted approach to address residual uncertainties related to PK, efficacy, safety and immunogenicity. Owing to the species difference, investigation in animals will not adequately address the residual uncertainties related to PK and PD, but it might identify any substantial differences between the proposed biosimilar and the reference product. Regardless of whether differences are observed, the value of animal PK and PD investigations is limited and does not negate the need for the quantitative data derived from PK and PD studies in humans [7].

Similarly, immunogenic assessment in animals is not necessarily predictive of immunogenic responses to protein products in humans, because animals can be overly reactive to human protein [7]. In addition, animal studies typically involve a small number of animals, thus making it difficult to draw conclusions on the comparison of immunogenicity between the proposed biosimilar and a reference product. Despite these limitations, immunogenicity assessment in animals adds value during the development of a biosimilar agent. For example, significant differences in the immune response profile in inbred strains of mice can indicate the proposed biosimilar and reference product differ in one or more product attributes not previously identified. If identified, this information could inform the design of the immunogenicity assessment in humans [7].

The question of ‘how similar is similar enough’ must be considered in the context of the time and resources needed to resolve uncertainties. As a general principle, uncertainties remaining after completing early clinical development should be those that can be resolved only with a Phase III clinical trial of efficacy, safety and immunogenicity. Statistical approaches should be considered when determining the similarity of the proposed biosimilar to the reference product. For example, the biosimilarity index assesses the probability that the observed significant result from a clinical trial is reproducible [17]. It uses a stepwise process that is robust to the study endpoints, criteria and study designs [18]. Scientific- and risk-based approaches to resolving uncertainties to an acceptable level in any given clinical setting are a key principle of the FDA guidelines [16].

**Targeting the profile of the proposed biosimilar product**

The profile of the reference product and others within the same class, if any, is another consideration in designing early clinical studies. For example, if the PK of the reference product is known to be different among different subpopulations, conducting the PK similarity study of the proposed biosimilar in a representative but sensitive and homogenous subpopulation will provide a clearer comparison of the intrinsic PK properties for the proposed biosimilar and the reference product. Comparisons of the interactions with various factors affecting the PK between the proposed biosimilar and the reference product can be further assessed in a larger Phase III trial in the target patient population using a population PK approach.

**Stakeholder perspectives and needs**

Increased patient access is a factor stimulating biosimilar development. A survey conducted by the National Comprehensive Cancer Network (NCCN) found that stakeholders, including physicians, nurses and pharmacists, had a high interest in prescribing, dispensing and administering biosimilars [19]. This and other surveys have found that stakeholders want to understand the concepts related to biosimilar development and the regulatory process involved. Currently, this knowledge often is limited [19,20].

Unlike generic small molecules, where adoption by hospitals is often without formal review by the Pharmacy & Therapeutics Committee, the NCCN survey, which included 277 participants in the 16th annual NCCN congress (physicians, nurses, pharmacists and other clinicians and nonclinicians from the USA and around the world), found the majority of respondents would require a review and discussion before using a biosimilar [19]. Moreover, two-thirds of respondents indicated information about PK was very important and three-quarters indicated Phase III clinical studies directly comparing the safety and efficacy of the biosimilar with the reference product were very important [19].
Stakeholders are looking for clinical results showing a biosimilar product is highly similar to the reference product without unexpected side-effects or other complications [19–23]. Specifically, the need for safety data was shown in the results of a recent European Crohn’s and Colitis Organisation survey of nearly 275 members [24]. The majority of respondents were aware that biosimilar monoclonal antibodies are not the same molecules as the reference product, with nearly seven of ten citing immunogenicity as their main concern. These considerations must be balanced by the fact that unwanted immunogenicity is a risk with any new biological product and is not specific to biosimilars. In addition, advances in science could mean the methods used to assess immunogenicity by biosimilar sponsors could be more sensitive than those used for the reference product at the time of approval. Early clinical studies provide a means to evaluate not only comparative PK and PD but also initial assessment of immunogenicity. Interchangeability and automatic substitution also are important considerations to healthcare providers [22], and there is a diversity of opinion regarding how these issues should be addressed.

PK and PD

A study to demonstrate the PK similarity between the proposed biosimilar and the relevant reference product is a key component of the early clinical development of a biosimilar program. The primary objective of this study is to compare the intrinsic PK properties of a proposed biosimilar with the reference product. In the cases when PD markers are available, comparative PD assessment can be added as a study objective.

A key question in designing the PK similarity study is whether to conduct the study in healthy volunteers or patients with the disease that is relevant to the target indication. The choice of the PK study population should take into account factors including prior clinical experience of the reference product, sensitivity to detect intrinsic differences in PK and variability of PK among the candidate populations. If safety differences compared to the reference biologic are not a concern, healthy subjects generally are preferred for the PK comparability study because this population can be associated with fewer complicating factors that affect PK (e.g. disease status, concomitant medications) than patient populations, thereby representing a relatively homogeneous population to compare intrinsic PK properties sensitively. The healthy subject population could have a different immune response to the treatment than disease populations, because patients can have altered immune status owing to their disease or the need to receive concomitant immune-modulating medications. In cases where the development of antidrug antibodies can substantially alter the PK and thus affect the PK assessment, conducting the PK comparability study in a less immunogenic population might be desirable. In cases where the safety profile of the product does not allow a study in healthy subjects, the PK similarity will need to be assessed in an appropriate patient population in which the disease state is consistent with the indication for which the proposed biosimilar is being developed [25,26].

For the PK comparability study, a parallel design generally is needed when the elimination half-life of the proposed biosimilar is long. A crossover design can be used when the elimination half-life of the biosimilar is short (e.g. fewer than five days), the incidence of immunogenicity is expected to be low or there is known inter-subject variability in PK with the reference product [7]. In a crossover design, subjects are randomized to receive the biosimilar or reference product sequentially during the first treatment period followed by the alternative treatment during the second treatment period, with a washout between the two treatment periods [27].

The dose and route of administration used in the PK investigation should be those determined to be the most sensitive to detect differences in PK between the proposed biosimilar and the reference product [7]. When multiple therapeutic dose levels are used for the reference product, a low dose might be more sensitive than a high dose for detecting differences in the target-mediated disposition involved in the distribution and elimination mechanisms for some biologics [28]. If the biosimilar can be administered intravenously and subcutaneously, PK studies using the subcutaneous route generally are sufficient because absorption and elimination characteristics can be evaluated [15].

For a single-dose study, key parameters for the PK similarity assessment will include the maximum drug concentration (Cmax), area under the concentration–time curve (AUC) from zero to the last time point with measurable concentration (AUC0–t), and AUC from time zero extrapolated to infinite time (AUC0–∞). For a multiple-dose study, the key PK parameters will include Cmax, AUC within one dose interval (AUCτ) and the trough concentration (Ctrough) under steady-state conditions [7,15]. PK similarity of the proposed biosimilar to the reference product will be established through bioequivalence testing of the key PK parameters, using predefined acceptance criteria [29]. When the acceptance criteria of PK similarity are not met, investigations will be needed to determine whether the observed difference is due to study design limitations or to differences in intrinsic PK properties. Additional assessment will be needed to address the residual uncertainty in PK and determine the clinical meaningfulness of the observed difference.

Whenever a clinically relevant PD marker is available in the population selected for the PK comparability study, comparative assessment of the PD effect also can be considered as part of the objectives for the PK similarity study. Investigation of the PD profile of a biosimilar can add value to the totality of evidence for demonstrating biosimilarity and reduce the residual uncertainties after the early clinical development. When the PD marker is involved in the mechanisms-of-action shared by multiple indications, the PD data could also be used as strong evidence to support the extrapolation across approved indications of the innovator product beyond those selected for the Phase III testing for the proposed biosimilar. Furthermore, the comparative PD data are especially valuable when the PD endpoints are more sensitive than the efficacy or safety endpoints of the Phase III trial in detecting small differences between the proposed biosimilar and the reference product. In specific cases (e.g. for structurally less complex biosimilars) the EMA and FDA note that addition of comprehensive PD data to PK and other investigations that convincingly demonstrate high similarity between the biosimilar and reference product could obviate the need for a comparative Phase III clinical efficacy and safety study [6,7].

Key criteria for selection of PD measures include the following: (i) relevance to clinical outcomes; (ii) ability to be assessed after a sufficient period following dosing with appropriate precision; and
(iii) availability of assays with appropriate sensitivity to detect clinically meaningful differences between the proposed biosimilar and reference product [7,15]. Examples might be the hemoglobin level with epoetin alfa or the American College of Rheumatology 20% response rate with infliximab. Although uncommon, the inclusion of PD data where there is an established association between the PD endpoint and clinical efficacy can add support to the determination of similarity and provide added support for a selective and targeted approach to later clinical Phase III safety and efficacy studies [7,15]. In some cases, sensitive and clinically important PD endpoints or assays are not available. If this occurs, discussion with regulatory agencies might be appropriate. In addition, a combination of markers that assess different domains of activities and are based on sound pharmacologic principles, including dose-concentration sensitivity, can provide sufficient evidence to assess clinical comparability [7,15].

**Clinical safety and immunogenicity**

PK and PD studies conducted at the early clinical development stage are not designed to compare the safety and immunogenicity of the proposed biosimilar with the reference product, especially when these studies are not conducted in the therapeutic setting. Nevertheless, the safety and immunogenicity data gathered from these studies are valuable in the context of biosimilarity determination. Observation of a substantial difference in the safety or immunogenicity profiles could help identify potential product differences, providing information to guide the design and conduct of the Phase III trials.

The scope of investigations related to clinical safety is dependent on residual uncertainty regarding the proposed biosimilar, as well as safety concerns, if any, related to the reference product and its class [7,15]. To assess safety, the type, severity and frequency of adverse reactions observed with the proposed biosimilar are compared with those observed during the clinical use of the reference product. Safety related to infusion-related reactions and immunogenicity is an important consideration because of the immunogenic potential of all biologics and the potential impact of immune responses on safety and efficacy [7,15].

For the PK and PD studies conducted in early development, the goals of immunogenicity testing are severalfold. The first is to monitor the incidence and severity of human immune response to the treatment, especially if these are the first studies of the proposed biosimilar being given to humans. Although the sample size of these studies might be limited, they could identify the substantial differences, if any, in immunogenicity properties between the products so as to inform the nature and extent of immunogenicity investigation during Phase III clinical development [7,30,31]. Second, information about the presence and magnitude of antidrug antibodies and neutralizing antibodies will help evaluate if the PK or PD assessment is affected by the development of immune response. It is known that the formation of antidrug antibodies can alter the PK behavior of the drug molecule. Third, the immunogenicity assessment in early trials can help evaluate performance of the immunogenicity assays for analyzing clinical samples, providing valuable data to support the use of adequate assays for testing samples from the comparative immunogenicity assessment in Phase III trials.

The assessment of immunogenicity in early clinical studies can be conducted using the same assay format and sampling schedule for the proposed biosimilar and reference product. Assays capable of sensitively detecting immune responses, even in the presence of circulating drug product, might need to be developed [7]. The assay strategy follows a tiered approach of screening, confirmation and titer determination. The samples confirmed as positive for antidrug antibodies are further tested for the neutralizing capacity of the antibodies [31,32]. The immunogenicity assessment endpoints in the early clinical trials include antibody titer, time course of development, persistence, disappearance and association with clinical sequelae [7].

**Assessment of the early clinical development program**

A final task in the early clinical development of a biosimilar product is to determine whether the objectives of the early clinical development program have been achieved and the extent to which uncertainties remain regarding similarity with the reference product [7]. Remaining uncertainties that do not require a Phase III clinical trial for resolution could be addressed using a targeted approach in further early clinical development.

**Summary and concluding remarks**

Clinical development of a biosimilar is a stepwise process that includes early clinical investigations in humans. Clinical investigation standards needed to demonstrate that a proposed biosimilar is highly similar to the reference biological product are based on guidelines from the EMA and FDA. Although these guidelines share some similarities, there are important differences between them, for example, the statutory ability of the regulatory agency to define an interchangeable biosimilar, as well as differences in the approach to in vivo clinical data requirements. Furthermore, these guidelines continue to evolve as more biosimilar products are submitted for regulatory approval and considerations associated with clinical development (such as appropriate compound nomenclature and labeling of biosimilars) are identified.

Strategically designed early clinical studies can address the residual uncertainty following nonclinical investigations and guide a selective and targeted approach to Phase III clinical trials. For biosimilars, the uncertainties addressed by early clinical studies are related to PK, PD and, to a lesser degree, safety and immunogenicity in humans. The PK comparability assessment should be conducted in a relatively homogeneous population and under sensitive conditions. Comparative PD assessment can add value to the biosimilarity determination, leading to a targeted approach in Phase III investigations. Evaluation of safety and immunogenicity as secondary objectives in PK and PD studies can identify substantial differences in the proposed biosimilar and the reference product. The immunogenicity assessment in early-stage studies can help evaluate adequacy of the immunogenicity assays to be used for sample analysis in Phase III trials. These extensive clinical evaluations in early-phase studies can allow a more targeted Phase III clinical program and approval process for a given biosimilar.
Most recent FDA draft guidance for industry: clinical pharmacology data to support a demonstration of biosimilarity to a reference product

The Guidance for Industry: Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product, issued by the FDA in May 2014, is the fifth and latest in a series of draft guidances to industry that the FDA is developing to implement the Biologics Price Competition and Innovation Act of 2009 [38]. This draft guidance provides additional detail on the use of clinical pharmacology studies to support biosimilarity and focuses on three key concepts [38]:

- Exposure and response assessment
- Evaluation of residual uncertainty
- Four tiers relating to analytical quality and similarity (not similar, similar, highly similar and similar with fingerprint-like similarity)

The draft guidance describes the value of exposure–response data for pharmacokinetic (PK) assessments or pharmacodynamic (PD) markers in demonstrating no clinically meaningful differences between a proposed biosimilar and a reference biologic [38]. As described in previous guidances, biosimilar development uses a stepwise, risk-based comparability exercise to resolve residual uncertainty regarding the similarity between the proposed biosimilar and the reference biologic. In its review of the biosimilar data package, the FDA uses a ‘totality of the evidence analysis’ [38].

Although not part of clinical development, the key role of comparative structural and functional studies to inform clinical development is detailed [38]. The FDA introduced the concept of four assessments that could result from the comparative analytical characterization: ‘not similar,’ ‘similar,’ ‘highly similar’ and ‘highly similar with fingerprint-like similarity’ [38]. These tiers relate to analytical similarity. The ultimate goal is to achieve the statutory standard for analytical similarity (highly similar) that allows approval of the product as a biosimilar as per the 351(k) pathway when supported by other appropriate data [38]. The greater the level of analytical similarity achieved the more targeted the clinical data package can be [38]. The tiers are intended to form a point in time assessment that can change when more data are generated to compensate for residual uncertainty [38]. The importance of comparative PK/PD assessments to resolve any residual uncertainty in the analytical similarity is highlighted [38].

Regarding the use of clinical pharmacology studies to support biosimilarity, the importance of using appropriate bioanalytical methods to evaluate the PK and PD properties is emphasized, with considerations given to general assay selection [38]. The benefits and limitations of specific assays (i.e. ligand binding, concentration and activity) and considerations for PD assay selection are described [38].

The clinical pharmacology studies should also collect safety and immunogenicity data [38]. The assessment of safety and immunogenicity should consider published data regarding the reference biologic including those related to the time-course of the safety signals or immune responses [38]. Several other considerations are noted, including the selection between crossover and parallel study designs used to evaluate clinical PK and PD similarity, the requirement to use the US-licensed reference product or establish bridging to the US-licensed reference product and the relevance of specific characteristics of the proposed biosimilar in selecting the study design (study population, dose selection, route of administration) [38]. The PK endpoints for the different study design (single- vs multiple-dosing) and different routes of administration (intravenous and subcutaneous routes) also are discussed [38]. Extensive information is provided regarding how human PD data can be used to assess the clinically meaningful differences and address the residual uncertainty and the design considerations for the PD assessment (e.g. sampling time points and duration, PD endpoint for comparison) [38]. Statistical evaluation of PK and PD results is based on: (i) a criterion to allow the comparison; (ii) a confidence interval for the criterion; and (iii) an acceptable limit [38].

The current draft FDA guidance addresses the use of modeling and simulation tools when designing a PK and/or PD study [38]. These tools can be used to analyze publicly available data for the dose–response or exposure–response relationship of the reference biologic, or information generated by the sponsor using a small PK/PD study, to justify the biosimilar dose used in the study [38]. A similarity study with multiple dose levels to compare PK/PD between the proposed biosimilar and the reference product could also be considered when clinical pharmacology evaluation is likely to be the major source of information to assess clinically meaningful differences [38]. In addition, modeling and simulation can also be used to define the acceptable limits for PD similarity using publicly available information on biomarker–clinical-endpoint relationships [38].

Conflicts of interest

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