

Biosimilar development – an overview

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Abstract

Biosimilars are biological drugs that are similar to, and cheaper than other biological drugs (called “reference originator biologics”) that are already in use. They share an identical amino-acid sequence but, given the inherent variability of biological molecules, not full “sameness”. Biosimilar registration follows a strictly regulated pathway based on a totality-of-evidence approach. This article critically discusses the particulars of biosimilar development, including the continuous development of regulatory guidelines, familiarises readers with biosimilar-specific terminology, addresses the typical challenges of writing biosimilar dossiers, and summarises future directions in biosimilar development in the context of a changing competitive landscape. After reading this article, medical writers with different backgrounds, including those previously unfamiliar with key aspects of biosimilar development, should be able to better understand and apply these guidelines in their daily biosimilar work.

What are biosimilars? What are they not?

Biologics or biological drugs are products created from living organisms or that contain components of living organisms. Biosimilars are biological drugs that are similar to, and cheaper than, other biological drugs (called “reference originator biologics”) that have already been approved for use on the market. Since biologics



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and biosimilars are created in living cells, they cannot be chemically synthesised like conventional drugs and their generics.

While a biosimilar candidate and an originator biologic share the same amino-acid sequence, they can never be identical, due to the inherent variability of complex biological molecules. In other words, a biosimilar and its reference biologic share a similar (but never exactly the same) functional version of the active substance. Examples of biosimilars (and biologics) include monoclonal antibodies, hormones, small proteins, vaccines, and fusion proteins.¹ Biosimilars (and biologics) that are monoclonal antibodies or derivatives thereof target pro-inflammatory cytokines, most commonly tumour necrosis factor alpha.

In the EU, a biosimilar is defined as a biological medicine highly similar to another

biological medicine already approved in the EU, for which there are no clinically meaningful differences to the reference medicine in terms of safety, quality and efficacy.² In the US, a biosimilar product is defined as a biologic product approved based on demonstrating that it is highly similar to an US FDA-approved biologic product that has no clinically relevant differences in terms of safety and effectiveness compared with the reference product; only minor differences in clinically inactive components are allowed for a product to be deemed biosimilar.³ Other terms used to describe biosimilars are: follow-on biologic, follow-on protein, and subsequent entry biologic.⁴ An essential aspect to keep in mind is that the EU-approved and US-approved reference products are not considered equivalent by default.

Biological medicines (originator biologics



and biosimilars) offer treatment options for patients with chronic and often disabling conditions such as diabetes, autoimmune disease, and cancer.² Biologics have a 12-year exclusivity in the US⁵ and an 11-year exclusivity in the EU, comprising 10 years for new biologics (eight-year data exclusivity and two-year market exclusivity) and a one-year extension for a new indication.⁶

A biosimilar candidate can be manufactured and (once biosimilarity to an originator has been shown) sold at a lower cost than the originator biologic, as the clinical development programme for a biosimilar is lean and relies heavily on the efficacy and safety experience previously established with the originator. Thus, it can be beneficial for patients with chronic conditions to gain access to biosimilar medicines at prices more accessible than those of their originator biologics, and profitable for companies to specialise in

biosimilar development. Biosimilars have been on the market for 13 years in the EU (the first approval of a biosimilar product in the EU was in 2006)² and for 4 years in the US (the first approval by the US FDA was in 2015).⁷

Regulatory aspects of biosimilar development

Since variability (be it qualitative or quantitative) may result not only in a loss of biological function, but also in severe and potentially unknown adverse events, biosimilars need to follow a highly regulated regulatory pathway. This pathway differs between the EU and the US.

Historically, regulatory requirements in the EU and US have developed in parallel with the

development of biosimilars. The regulatory framework for biosimilars was established in the EU in 2003. The Committee for Medicinal Products for Human Use (CHMP) overarching guideline on biosimilars came into force in 2005 and a revised version came into effect in 2015.⁸ In recent years, both the overarching guideline and its sister guidelines (that focus on quality, non-clinical, and clinical issues) have been updated, reflecting the growing experience with biosimilars. In recent years, the US FDA has also been heavily engaged in developing guidelines for biosimilar development⁹ and providing advice to stakeholders. In 2010, the World Health Organization published a “similar biotherapeutic products” guideline.¹⁰ Efforts towards global guidelines are however still in a very early stage. See Table 1 for further details.

Additionally, different health authorities currently prefer and use slightly different terminology. It is thus up to pharmaceutical companies to develop internal best practices with input from their regulatory affairs departments regarding terms acceptable for use in the EU, US, and the rest of the world.

Interestingly, because of the inherent variability of biologics, an originator manufacturer of biological products also faces challenges when introducing changes in the manufacturing process, and needs to demonstrate equivalence, for example, for different formulations of the same medicinal product. Changes in the regulatory requirements intended primarily to support and facilitate changes to biologics’ manufacturing processes triggered the evolution of the concept of the biochemical bridge, whereby a comprehensive analytical (biochemical and biophysical) comparative testing programme could be used as part of the justification for demonstration of equivalence or similarity.⁴ The biochemical bridge easily lent itself to the analysis of candidate biosimilars and played an important role in starting to define

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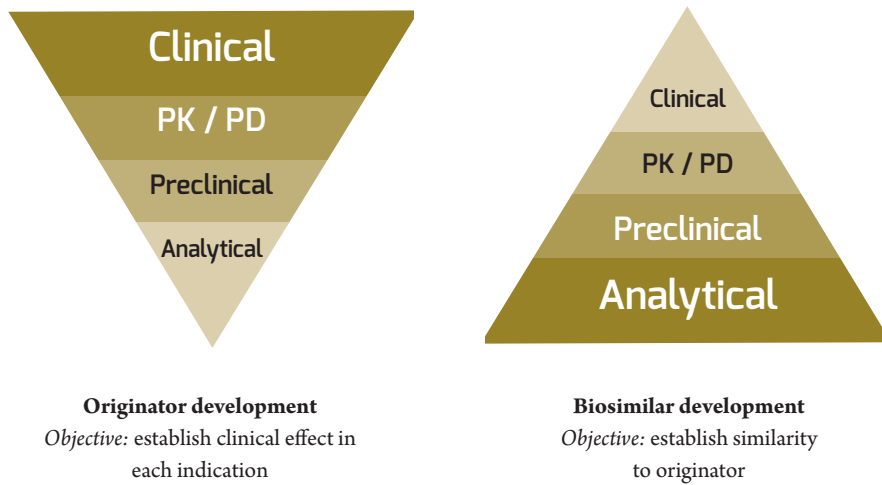


Figure 1. Biosimilar vs. originator development – the world upside down

PK = pharmacokinetics; PD = pharmacodynamics.

differences and their correlations to physiological and clinical effects (see section **The world upside down** below).

The EU-approved and US-approved reference products are not considered, by default, similar to each other and thus it is essential that studies aiming to establish similarity use the reference biologic matching the intended target region. In practice, in a lean

Paediatric development requirements for biosimilars differ between the EU and the US.

development programme, this often means that both reference products will be included in the same clinical study, and the equivalence of the biosimilar candidate will be tested against both.

Paediatric development
Regulatory requirements for paediatric biosimilar development differ between the EU

and the US. In the EU, Regulation (EC) No 1901/ 200 exempts manufacturers of candidate biosimilars from providing a paediatric investigational plan (PIP).¹¹ In contrast, according to the 2016 revised US FDA draft guidance on PSPs,¹² a paediatric study plan (PSP) is needed for candidate biosimilars in the US.¹³

The world upside down

Biosimilarity to a reference product (biologic originator) is established based on a so-called totality-of-evidence approach. The bulk of a biosimilar development programme is made of comprehensive analytical (biochemical and biophysical) comparative testing as part of the justification for demonstration of equivalence or similarity, while the clinical part is – especially when looking at it with an originator mindset – very lean (see Figure 1). Residual uncertainties need to be addressed.

Biosimilars follow a step-wise development, with the risk of failure decreasing at each step:

- **quality comparability** is essential and involves comprehensive characterisation and comparison of physicochemical and biological properties; the degree of similarity demonstrated at this level might determine the amount of additional evidence that needs to be generated at later stages; for further information on quality attributes requirements by region,^{14,15} see Table 1.
- **pre-clinical (functional) comparability**

Table 1. Biosimilars in the EU and in the US – a selection of key differences

Topic	EU	US
Definition ^{2,3}	A biological medicine highly similar to another biological medicine already approved in the EU, for which there are no clinically meaningful differences to the reference medicine in terms of safety, quality and efficacy	A biologic product approved based on demonstrating that it is highly similar to a US FDA-approved biologic product, and has no clinically relevant differences in terms of safety and effectiveness compared with the reference product; only minor differences in clinically inactive components are allowed
Quality attributes ^{14,15}	EMA Reflection paper on statistical methodology for the comparative assessment of quality attributes in drug development	US FDA Guidance for Industry: Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
Animal studies	Focus on <i>in vitro</i> studies	Animal studies required
Paediatric development ^{11,12,13}	PIP not required	PSP required
Reference product	EU-approved originator biologic	US-approved originator biologic

EMA = European Medicines Agency; EU = European Union; US FDA = United States Food and Drug Administration; PIP = paediatric investigational plan; PSP = paediatric study plan; US = United States.

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offers reassurance on similar effects and involves functional *in vitro* assays to define and compare the mode(s) of action:

- **in vitro studies** are always required and normally cover most functional aspects.
- it is essential to determine **the level of concern** depending on quantitative/qualitative differences in critical quality attributes.
- **in vivo PK (pharmacokinetics)/PD (pharmacodynamics) and/or safety studies** may be necessary in case of e.g., a new expression system; see Table 1 for details by region.
- **clinical comparability** involves testing in a sensitive population and dose at a sensitive time point using an appropriate statistical model and testing approach; usually the details for phase III conduct are agreed upfront with the health authority of the region intended for registration.

Clinical biosimilar development

Unlike in originator drug development, clinical programmes for biosimilar candidates are lean and rely on the clinical experience with the originator biologic. Most of these programmes only comprise:

- one phase I PK/PD bridging study in healthy volunteers.
- one phase III confirmatory efficacy and efficacy study in patients with the most sensitive indication; switching treatment groups is usually included in the study design.

The objective of both types of studies is to show equivalence between the proposed biosimilar and its corresponding originator product, for which a solid justification for the applied equivalence margins is required. For generics studies, a 90% confidence interval within 80%–125% equivalence margins is acceptable for demonstrating bioequivalence, on the assumption that the generic and originator medicines will have the same behaviour in the body once absorbed. For biosimilarity, however, a different confidence interval may be needed to demonstrate similarity in exposure; this needs to be discussed and justified. For generics, the focus is on comparing the absorption of the test and reference products, while for biosimilars it is of interest to determine a potential difference both in the absorption and the elimination phase.

As already mentioned, when running global development programmes and designing clinical

studies, it is to be kept in mind that the EU-approved product and the US-approved product are not by default equivalent, and that the equivalence margins and confidence interval requirements may differ between regions. In addition, what is considered the most sensitive indication (to show differences) and the most sensitive population within this indication is usually agreed upon upfront with the respective health authorities before running a comparative clinical efficacy and safety study.

Biosimilar studies do not test for superiority.

An equivalence design at the 90% or 95% confidence interval is used in phase III comparative trials (generally preferred to a non-inferiority design) and establishes that the biosimilar is neither superior nor inferior to the reference product.¹⁶ For detailed statistical considerations in biosimilar development, see Balfour and Schmitt in this issue.¹⁷

Dose-ranging studies are not conducted in biosimilar development, as a biosimilar candidate will be approved for the specific approved dose(s) of the originator once biosimilarity has been shown and extrapolation has been scientifically justified (see below for further details). Additionally, in the case of manufacturing

Clinical programmes for biosimilar candidates are lean.

Table 2. Interchangeability and substitution in the EU and in the US – key differences¹⁸

Topic	EU	US
Legal basis Interchangeability	European Commission Consensus Document “The medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber”	2009 BPCI Act The medical practice according to which “the biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product”
Substitution	An administrative measure defined as the practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber	An interchangeable product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product
Decisions on interchangeability and switching	Can only be reached at national level by individual states; the EMA does not have the authority to make such decisions. Thus, pharmacy-level substitution is not routinely practised in the EU.	Individual US states control pharmacy-level substitution; the US FDA may approve a product as interchangeable/switching; 35 US states have passed legislation addressing substitution.

BPCI = Biologics Price Competition and Innovation; EMA = European Medicines Agency; EU = European Union; US = United States; US FDA = United States Food and Drug Administration.

changes during the course of development of the biosimilar candidate, bridging studies between formulations are needed to establish their equivalence (just as they are needed for biological originator manufacturers in such situations) to ensure function preservation given the inherent biological variability of biologics.

Immunogenicity

Immunogenicity is a major safety concern (manifesting as hypersensitivity reactions) not only for biosimilars, but for the development of biologics in general. The development of antidrug-antibodies (in particular neutralising antibodies) could also impact efficacy (potentially resulting in a decrease or loss of efficacy), therefore clinical design and corresponding documents need to address such concerns. Antibody formation takes time, thus one-year immunogenicity data are required for most monoclonal antibody applications in the EU.

Previous knowledge about the immunogenicity of the originator biologic is valuable, nonetheless the immunogenic potential of small differences in quality attributes of the biosimilar candidate may not be easy to predict or understand. Methods for antibody detection are becoming increasingly

sensitive, thus it is often challenging to meaningfully compare data with the candidate biosimilar with historical data provided in the label of the originator biologic.

Overall, the biosimilar candidate should have the same safety profile as the originator biologic. Lower immunogenicity (and thus improved safety) could be accepted, whereas higher immunogenicity cannot. In cases of lower immunogenicity, however, efficacy could look artificially higher due to lower levels of neutralising antibodies and entail higher rates of other adverse events. This could nonetheless be accepted, provided that patients without anti-drug-antibodies show comparable efficacy.

Extrapolation

An essential concept for biosimilar development is the extrapolation to other indications. Once biosimilarity has been established based on the totality-of-evidence, extrapolation from the studied indication to all indications approved for the reference biologic is possible based on solid scientific justification.

In other words, extrapolation is the term used to describe the use of a biosimilar for an indication approved for the originator that was

not directly tested in the development programme of the biosimilar.⁴ Efficacy and safety do not need to be established *de novo* in each indication of the originator biologic, but a solid rationale is needed and extrapolation is granted on a case-by-case decision for each biosimilar. Key factors for the scientific rationale are usually a shared clinically relevant mode of action across indications, and the sensitivity of the studied indication and its relevance for other indications.

Once biosimilarity has been established based on the totality-of-evidence, extrapolation from the studied indication to all indications approved for reference biologic is possible based on solid scientific justification.

Interchangeability, substitution, and switching

Following the approval of a small molecule pharmaceutical product, being able to switch (or substitute) between pharmaceutical drug products (from originator to generic) is a well-



established and extensively used practice and is typically implemented at the pharmacy level. However, in addition to restrictions against biosimilar extrapolation, this type of switching (between originator and biosimilar) and interchangeability requires approval at the national level in the EU. The terms “interchangeability”, “substitution”, and “switching” all refer to the practice of treating patients with the originator biologic and then changing treatment to an approved biosimilar, or changing from one approved biosimilar to another approved biosimilar.^{4,18} There are a number of differences with which the EMA and the US FDA regard the interchangeability of biologics and biosimilars, as detailed in Table 2.

What writers working on biosimilar documents need to know

When working on biosimilar documents, writers should pay particular attention to the major key challenges described in Table 3.

For further relevant details and practical tips for the daily work of medical writers, see Brauburger and Heisel-Stöhr (focus: clinical study reports [CSRs] and common technical documents [CTDs]);¹⁹ Prechtel et al. (focus: pharmacovigilance documents),²⁰ and McMinn et al. (focus: lay summaries)²¹ in this issue of *Medical Writing*.

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Biosimilar development – what’s next?

“First wave” biosimilars (growth hormones and monoclonal antibodies) were vastly more complex than pharmaceutical preparations, yet relatively simple biological molecules. Biosimilars with more complex structures are currently under development, with multi-subunit, extensively post-translationally modified, and lipid-containing products; such products may raise new complications and concerns.⁴

In addition, the competitive biosimilar landscape is changing. A number of new companies have recently entered the biosimilar development scene and they are making fast progress. With speed-to-market being an essential factor for profitable biosimilar development, traditional key players/pharma giants that were once pioneers in the field may strategically opt out from pursuing certain biosimilar development

programmes,²² as their new competitors cut their way forward. With most monoclonal antibodies coming off patent by 2020 and given the introduction of biosimilars, existence of their originator biologics, and creation of biobetters (improved versions of the originator biologics), the oncology landscape and its key stakeholders (prescribers, pharmacists, nurses, patients, reimbursing bodies, and manufacturers) will be facing many challenges.¹ Several older challenges remain: the acceptance of biosimilars by the general public and their ample use in health care; a better understanding of the impact of differences in quality attributes on clinical efficacy and safety;^{14,15} a meaningful approach to collecting post-marketing safety data from biosimilars and their reference biologics; and efforts to globally converge regulatory requirements, including the potential use of a global reference product.

Conclusion

The world of biosimilars brings exciting opportunities for professional medical writers. As a new wave of biosimilars is currently under development, and regulations in the EU and the US are simultaneously becoming increasingly more complex, teams working on biosimilar development will need increasing guidance. Medical writers can play an important role in the efficient development of biosimilar documents

Table 3. Key challenges in writing biosimilar clinical documents and how to address them

Challenge	Situation	Way forward
The similarity mindset challenge (toughest)	We are creatures of habit who like to stick to familiar ways of doing (i.e., writing) things and usually it takes time for teams with an originator mindset to shift to the biosimilar mindset. In this context, clinical teams have a tendency to over-interpret minor treatment differences throughout the results sections, yet still tend to conclude “similar safety profiles”.	Writers should remind teams that the main goal of the biosimilarity exercise is to establish similarity to an already established product, not a treatment advantage compared with the standard of care. The efficacy and safety of a biosimilar candidate do not need to be demonstrated de novo, this has already been done for the originator biologic. Minor safety differences between treatments in rather small populations of patients in phase III trials should only be discussed extensively if confounders can be meaningfully attributed and the differences are clinically relevant and raise a true concern.
The multiple treatment periods and multiple database locks challenge (moderate and very time-consuming)	For comparative efficacy and safety phase III trials in patients, multiple treatment periods and interim database locks (DBLs) are the norm. After a certain treatment period, patients are switched to a different treatment (e.g., from originator biologic to biosimilar candidate). Data cleaning issues may arise after such an interim DBL and often, teams spend hours discussing how to best address it.	Ideally, companies have learnt their lesson and have developed best practice guidelines for dealing with such instances, which are not at all uncommon. If not, medical writers should encourage the development of best practices both in terms of dealing with data cleaning issues with impact on attributing patients to patient sets, and in terms of standardising the way new data will be added to the clinical package once available: in the form of a revised clinical study report (CSR) including all data and treatment periods; amendments, CSRs that only focus on data from specific treatment periods etc.
The consistency challenge (moderate)	If the similarity exercise is generally successful, the wording in the proposed biosimilar label will be the same as in the originator’s label. Teams often think of new key messages to include in documents as development progresses.	All documents within a clinical development programme should build into the extrapolation concept so that similarity can be concluded based on the totality of evidence. Messaging consistency across clinical and pre-clinical documents in the same programme is essential, and so is addressing any residual uncertainties. Medical writers should remind teams of this whenever discussions seem to drift off.
The redundancy challenge (moderate)	While complexity in terms of “writing volume” for Modules 2.7 and 2.5 may look low (often there are only 2 studies and no pooling), these documents are crucial for the submission. Teams often like to repeat the same level of detail across all clinical documents.	Only key data should be presented in Module 2 documents, with cross-references to the more detailed presentation in the individual CSRs. Medical writers should: <ol style="list-style-type: none"> a) remind their teams that the CSRs are just one click away b) establish biosimilar-dedicated document templates within an organisation, as documents will need to be structured differently than those for originators, in order to be fit-for-purpose.
The multiple therapeutic areas challenge (easiest)	Biosimilars are commonly developed for use in the therapeutic areas immunology (for treating chronic autoimmune diseases such as psoriasis, psoriatic arthritis, Crohn’s disease, ulcerative colitis, psoriatic arthritis, ankylosing spondylitis, rheumatoid arthritis, and juvenile idiopathic arthritis), oncology, and endocrinology (insulin analogues and growth hormone analogues).	Medical writers should be familiar not only with regulatory and preferred wording requirements for biosimilar development in the target registration region, but also with treatment guidelines specific to the indication selected for phase III development. The good news for medical writers in terms of volume of work: only data for one indication need to be presented, unlike for originator biologic applications. Extrapolation to other indications approved for the biologic originator is possible and within the scope of the similarity exercise, based on the totality of evidence and a solid scientific justification.

that are fit-for-purpose, both by proactively helping establish best practices for the writing of such documents and by generally driving the shift from an originator to a biosimilar mindset.

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Conflict of interest

The author declares no conflict of interest.

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