Writing biosimilar clinical study reports and submission documents – what to expect and what to consider

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Abstract

With the emergence of biosimilars, the development process for these drugs is a topic of increasing interest to medical writers. Even though information and educational documents on the concept of biosimilarity are increasingly publicly available, it takes some practice for the medical writer to translate the specific requirements into fit-for-purpose documents. This feature article summarises the relevant regulatory requirements for the clinical development of biosimilars. It includes best-practice recommendations on how these requirements can be translated into the everyday work for medical writers.

Introduction

With the emergence of biosimilars, the development process for these drugs is a topic of increasing interest to medical writers. The common goal of a biosimilar development programme is to show that a biological medicine, the proposed biosimilar product, is "highly similar to another already approved biological medicine".[1] The latter is referred to as the originator product in this feature article. This similarity to the originator product is to be established not only in terms of quality characteristics and biological activity, but also in terms of safety and efficacy.[2] The main documents showing this similarity in clinical safety and efficacy are the clinical study reports (CSR) and the clinical summary documents included in the Common Technical Document (CTD). This article outlines the most currently available guidance and provides insight into typically occurring questions and problems faced when developing the clinical documents for a biosimilar development project.

Biosimilar CSR preparation

CSRs for studies included in clinical biosimilar development programmes should be authored the same way as any other CSR, following the common applicable guidance, such as ICH E3 and the ICH E3 Questions and Answers document.[3,4] Additional resources used for the authoring of CSRs, e.g., the CORE reference or the TransCelerate Common CSR Template can be referred to as well.[5,6] However, a number of biosimilar-specific topics exist that must be considered when writing a biosimilar CSR.

Study design and analysis

In biosimilar development, a minimum/standard clinical programme consists of a study investigating the pharmacokinetics (PK) and, if possible, pharmacodynamics (PD) of the proposed biosimilar (Phase I) and a confirmatory efficacy and safety study (Phase III).

The objective of both studies is to show equivalence between the proposed biosimilar and its corresponding originator product – equivalence either based on the PK/PD parameters, or based on efficacy, safety, and immunogenicity, depending on the type of the study. Consequently, each CSR needs to include a justification for the applied equivalence margins. This justification can be included as a reference to the respective protocol or statistical analysis plan, or as text directly in the CSR data-independent section (Section 9.7 as per ICH E3/CORE; Section 3.7 as per the TransCelerate Common CSR Template).

An important part within the concept of biosimilarity is to conduct the study in a sensitive indication; therefore, the chosen indication needs to be justified.[7] As the source for this justification is usually the protocol, the information can be added to the CSR either as a cross-reference to the protocol or as a brief summary (Section 9.3 as per ICH E3/CORE; Section 3.3 as per the TransCelerate Common CSR Template). In addition to describing the chosen sensitive indication, it is important to choose a sensitive population for the analysis. Whereas the intent-to-treat analysis set is the first choice for a superiority/non-inferiority study, biosimilar equivalence studies usually apply the per-protocol analysis set for the primary analysis (however, it is important to note that additional analyses on the intent-to-treat analysis set are always required).[8]

The primary objective of a biosimilar efficacy and safety study suggests a simple 2-group study design with the originator product as the comparator. However, the actual design of the study might be more complicated. The US concept of interchangeability requires studies to show that "the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch".[9] Therefore, biosimilar studies that are part of a global submission dossier often consist of several study periods with at least the originator product treatment group split into two groups, typically after the primary endpoint; a so-called switching study design (Figure 1). Note that this interchangeability concept is not applicable for other regions, such as the EU.

Even the design of a PK/PD equivalence study can become complicated if the study is planned to bridge two different regional originator products and, for example, if a three-way crossover design was applied.[8] No matter which development strategy or which study design has been chosen, the medical writer needs to pay close attention to the structure of the CSR to present the study data adequately.

As a non-adequately planned analysis cannot be rescued at the level of the CSR, the medical writer should already be involved during the planning of the study and (at the latest) during the development of the statistical analysis plan. Furthermore, the reporting of the study results often must allow for several interim database locks that might be needed depending on the sponsor's submission plans. It needs to be discussed upfront how all analyses are planned to be executed and how this translates into the sequence of one or more interim CSRs – for example, in terms of the sequence and numbering of the statistical outputs. If a long-term follow-up analysis for safety or immunogenicity is planned, an addendum to the final CSR might be needed. The number and sequence of CSRs also influences the resource planning, as blinded medical writers will have to be available after each unblinding event.

Interpreting and describing data

Development programmes for new biologic medicines usually comprise a number of clinical studies with a large number of patients required to conclude superiority or non-inferiority. In contrast, biosimilar development programmes usually comprise only a relatively small number of subjects needed to address an equivalence objective. Thus, especially in the safety assessment, a numerical difference of only one patient per group can lead to a large percentage difference between treatment groups. Therefore, assessing biosimilarity requires a clear understanding of whether these differences are clinically relevant or not.

When describing the data of the study, it is important to be aware that the overall safety and efficacy of the drug had already been established during the clinical development of the originator product. Therefore, the main goal of biosimilar clinical documents is to show that the proposed biosimilar is similar to the originator product in all aspects and *not* to establish the drug's efficacy or safety profile *de novo*. This is a fact the medical writer needs to keep in mind while writing, as inappropriate language easily obscures the scientifically appropriate message of the document (Table 1).

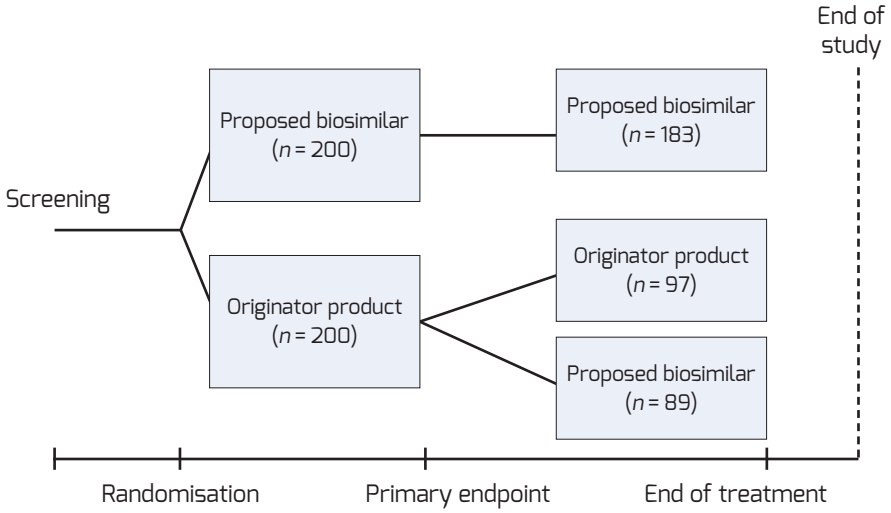

Figure 1. A typical study design of a biosimilar confirmatory efficacy and safety study
n = number of study participants per study group

Accordingly, the most important message in biosimilar documents is whether data in both study groups are similar.

No special focus on the overall results and no columns displaying total population results in in-text tables are required. If any general statement about the overall study population is needed, the text should typically refer to the end-of-text tables including the total column. Only when describing the subject disposition and referring to baseline characteristics, might some focus on the total characteristics remain; ultimately, the most important message is whether the biosimilar and the originator group performed similarly.

Immunogenicity

Immunogenicity is a topic not inherently linked to biosimilars alone, but in general to the development of biological medicines. In the CSR, immunogenicity is a separate topic that is often placed into the safety section (i.e., Section 12 as per ICH E3/CORE). However, it is important to note that anti-drug antibodies, especially neutralising antibodies, which inhibit the molecular function of the drug, also potentially influence the efficacy of the drug. Therefore, it is recommended to deal with immunogenicity either in both the efficacy and safety section, or in a separate new section dedicated to immunogenicity (for example Section 5.7 as per the TransCelerate Common CSR Template).

Biosimilar CTD documents

The fundamental premise underlying the development of a biosimilar is the establishment of similarity based on state-of-the-art analytics. This can take multiple iterations in early stage development and takes more time than would normally be required for an originator product. While the clinical development programme of an originator product is usually substantial, biosimilars require a tailored clinical programme. When illustrated graphically, this means the development programme of a biosimilar product resembles a pyramid, rather than the typically inverted pyramid usually shown for a standard development programme of an originator product (Figure 2).

These differences in drug development are reflected in the dossier structure, even though the submission dossiers for a marketing authorisation application of a biosimilar and an originator product use the same CTD structure and both development programmes include the same scientific topics.

Module 2

The overall goal in the overviews and summaries in Module 2 is to demonstrate similarity. However, we strongly recommend discussing the similarity of nonclinical and clinical properties in separate documents. The general CTD structure should be followed despite the need to establish the totality of the data/evidence. The individual

summaries and overviews should be focused and succinct and use smart cross-references rather than repetitions. With this document strategy, you will automatically follow the stepwise approach by showing:

- the analytical similarity, which justifies proceeding with the nonclinical programme, followed by
- the clinical programme that demonstrates PK/PD equivalence and similarity in efficacy and safety in a sensitive indication and population.

Modules 2.7.1 and 2.7.2

In biosimilar dossiers, Module 2.7.1 (Summary of Biopharmaceutics) and Module 2.7.2 (Summary of Clinical Pharmacology) are more important documents than in dossiers of new biologic medicines. PK/PD similarity is established and the biopharmaceutical testing strategy is discussed, both of which define the basis of the clinical development programme. Therefore, the medical writer should be involved at least in the review of these modules to ensure document consistency.

Modules 2.7.3 and 2.7.4

In the ideal clinical development of a biosimilar, one would expect one study per phase included in the dossier. Therefore, the Summaries of Clinical Efficacy and Safety are relatively short documents and can be co-developed with the CSRs. Close alignment of the content across the documents is key and having the same (lead) medical writers involved facilitates the document development.

The team should critically assess which analyses shall be reflected in the summaries and in which cases a cross-reference to the CSR would suffice. For example, not all study periods or analyses (subgroup/sensitivity) need to be copied from the CSR; only the most meaningful data should be summarised. Spending some time on mock tables, figures, listings (TFLs) and shell documents can accelerate the document development after database lock. Even mock text with an assumed similarity result can be drafted. Medical writers should use the time before database lock to establish rules on the use of terms such as similar/ comparable/ equivalent in a project-specific style guide.

Biosimilar dossiers usually do not include a formal Integrated Summary of Efficacy (ISE) or Integrated Summary of Safety (ISS) as, with essentially one study each in Phase I/III, data cannot be pooled meaningfully. Instead, the CSRs are the main source for clinical summaries. Of course, if more than one Phase I study is needed in the clinical development, the pooling of these studies may be supportive.

When planning an FDA submission without ISS and/or ISE, this topic should be discussed with the FDA upfront and the medical writer should be involved in the writing of the briefing book. Even if safety data are pooled, the ISS can be limited to the TFLs and the text part can be covered in Module 2.7.4. Make use of the options listed in the relevant guidance documents.[10,11]

Immunogenicity and extrapolation

Immunogenicity and extrapolation are both very important topics in the biosimilar dossier.

Immunogenicity can be described in dedicated sections of Modules 2.7.1 to 2.7.4 dealing with different aspects of immunogenicity. Alternatively, an Integrated Summary of Immunogenicity can be added to Module 5, so that all aspects of immunogenicity are summarised in a separate document to which Modules 2.7.1 to 2.7.4 provide meaningful cross-references. The team needs to decide on the strategy early on, taking into account the expected availability of the last immunogenicity data in relation to the planned finalisation timelines of all documents and the overall submission timelines.

A similar situation applies to the justification of extrapolation.[7] This topic can be covered in Modules 2.7.1 to 2.7.4, which in this case deal with different aspects of the extrapolation exercise. Alternatively, the entire extrapolation topic can be covered in Module 2.7.3 only or in a separate extrapolation document. If the team plans to expand the nonclinical data section of the extrapolation exercise, a separate document may be the preferred choice as it allows the other clinical documents (including writing and review) to remain focused. This separate extrapolation document can be added either to Module 5 or as an appendix to the Clinical Overview.

As the extrapolation topic is not foreseen in the standard CTD structure, there is some degree of freedom and creativity to help develop the best document strategy for the dossier and the submission plan. Extrapolation is a relatively new topic and we advise medical writers to check EMA and FDA homepages for already published dossiers, assessment reports, or briefing books before planning their own document strategy.

> ... the medical writer needs to pay close attention to the structure of the CSR to present the study data adequately.

Module 3 – as far as relevant for clinical documents

As outlined in the EMA Quality guideline, the biosimilar dossier should provide a demonstration of similarity.[12] This similarity exercise for a biosimilar product versus the originator product is an *additional* element to the usual requirements of the quality dossier. It should be discussed separately in Section 3.2.R of Module 3, in the Similarity Assessment Report.

If reference products of a different origin are used in the nonclinical or PK/PD studies as compared with the clinical efficacy and safety study, a justification for the bridging of the reference product in the latter study is required.[7,8] This justification should also be provided in Module 3.

When writing Modules 2.7.1, 2.7.2, or 2.5, cross-references to Module 3 will be needed. Hence, the medical writer should stay closely aligned with the Chemistry, Manufacturing, and Controls writer for consistency of the document contents.

Module 5

The bulk of documents in Module 5 are the CSRs and the bioanalytical reports. As discussed above, some additional documents may be added in Module 5.3.5.3, e.g. an Extrapolation Assessment Report, Integrated Summary of Immunogenicity, or a Statistical Overview to expand on statistical topics (such as the definition of the equivalence margin).

Biosimilar special documents/topics

Several topics in a biosimilar dossier need the medical writer's special attention:

- Justification for the equivalence margins: can be included in Module 2.7.2/2.7.3, in a separate document in Module 5, or as appendix to the Clinical Overview. The document strategy depends on the extent of the statistical modelling, which may be too extensive for inclusion in the CSRs or the summary documents.

Table 1. Differences in the description of endpoints between new biologic medicines and biosimilars

Topic	New biologic medicine	Biosimilar
Safety	Overall, out of 347 subjects, 110 subjects (31.7%) experienced at least one AE. The incidence of AEs in the test group was lower (50 subjects, 28.7%) than in the placebo group (60 subjects, 34.7%). The most common AEs were nasopharyngitis (test group: 25 subjects, 14.4%; placebo group: 27 subjects, 15.6%). More patients with back pain were reported in the test group (7 subjects, 4.0%) than in the placebo group (1 subject, 0.6%).	The proportions of patients with AEs were similar in each treatment group (biosimilar group: 50 subjects, 28.7%; originator group: 60 subjects, 34.7%). The proportion of patients with back pain appeared to be higher in the biosimilar group (7 subjects, 4.0%) than in the originator group (1 subject, 0.6%), but this difference was not considered clinically relevant.
Efficacy	At Week 16, the mean percent improvement in PASI from baseline was 80.9 for the test group and 8.1 for the placebo group. The PASI percent improvement from baseline to Week 16 between the test group and the placebo group (-72.8) was statistically significant with a p-value of <0.001.	At Week 16, the mean percent improvement in PASI from baseline was 80.9 for the biosimilar group and 83.1 for the originator group. The PASI percent improvement from baseline to Week 16 between the biosimilar and the originator group was -2.2 with a 2-sided 95% CI of (-7.4, 3.0). The 95% CI was within the equivalence margin of (-15, 15), indicating similarity / therapeutic equivalence between the biosimilar and the originator group.

Abbreviations: AE, adverse event; CI, confidence interval; PASI, Psoriasis Area and Severity Index

- Justification for the chosen sensitive population: needs to be included in the CSR in Module 5, in the clinical development section of the Clinical Overview, and in Module 2.7.3.
- Extrapolation across indications: can be rather extensive, depending on the list of approved indications of the corresponding originator product. It can be covered in Modules 2.7.1 to 2.7.4, in a separate document in Module 5, or as an appendix to the Clinical Overview.
- Comparison to literature: is usually requested by authorities. The team needs to align on the originator studies and/or other biosimilar studies that should be included in the comparison and on the cut-off date for this comparison. The comparison can be part of the Clinical Overview only or split across the Clinical Overview (brief summary) and the clinical summaries (a tabular presentation may be useful).
- Critical assessment on biosimilarity: should be provided in the Clinical Overview, but may also be added to Modules 2.7.2 to 2.7.4.

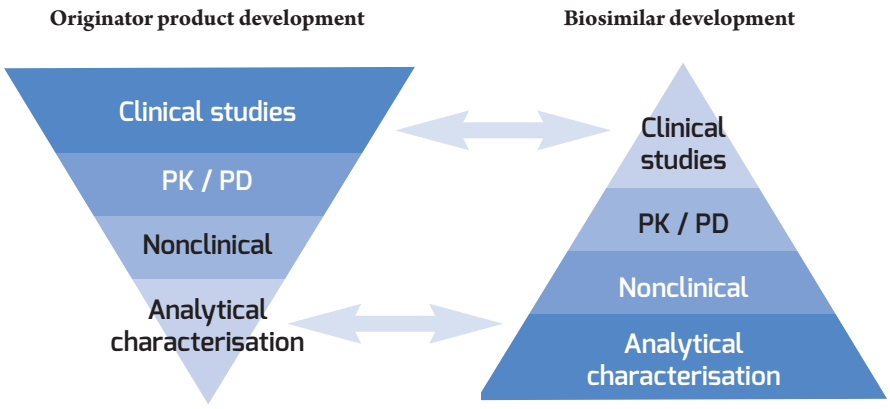

Figure 2. Inverted development pyramid showing the different foci during the development of a biosimilar compared with the development of a new biologic medicine.

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics. Source: adapted from [13]

Whether all of the topics listed above are relevant for the submission depends upon the nature of the proposed biosimilar product and on the originator product label. All documents need to be tailored to the needs of the product and a smart document strategy needs to be developed with the clinical submission team.

Summary and conclusion

Although information and educational documents on the concept of biosimilarity are increasingly publicly available, it takes some

practice to translate the specific requirements into fit-for-purpose documents, even for medical writers experienced in the drug development of new biologic medicines. It may be beneficial to develop separate templates for CSRs and clinical summaries in the CTD, or to request a waiver from the usual templates used for new biologic medicines to allow more flexibility with the document structures.

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Disclaimers

The opinions expressed in this article are the authors' own and not necessarily shared by their employers or EMWA.

Conflicts of interest

The authors declare no conflict of interest.

References

1. European Medicines Agency. Biosimilar medicines: marketing authorisation [cited 2019 Mar 01]. Available from: https://www.ema.europa.eu/en/human-regulatory/marketing-authorisation/biosimilar-medicines-marketing-authorisation.
2. Guideline on similar biological medicinal products: European Medicines Agency. Committee for Medicinal Products of Human Use (CHMP); CHMP/437/04 Rev 1.
3. ICH harmonized tripartite guideline. Structure and Content of Clinical Study Reports E3.
4. Structure and Content of Clinical Study Reports E3 Questions & Answers (R1): E3 Implementation Working Group.
5. Clarity and Openness in Reporting: E3-based. Version 1.0, 03-May-2016.
6. TransCelerate Biopharma Inc. Common CSR Template [cited 2019 Mar 01]. Available from: https://www.transceleratebiopharmainc.com/assets/common-protocol-template/.
7. Radovan D. Biosimilar development – an overview. Med Writ. 2019;29(2):20–7.
8. Balfour A, Schmitt S. Statistical principles in biosimilar development. Med Writ. 2019;29(2):28–32.
9. Guidance for Industry: Considerations in Demonstrating Interchangeability With a Reference Product: U.S. Food and Drug Administration. Draft guidance; 2017.
10. European Medicines Agency. Multidisciplinary: biosimilar [cited 2019 Mar 01]. Available from: https://www.ema. europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar.
11. US Food and Drug Administration. Biosimilars Guidances [cited 2019 Mar 01]. Available from: https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm444891.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery.
12. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues, Revision 1 – Adopted guideline: European Medicines Agency. Committee for Medicinal Products of Human Use (CHMP); CHMP/BWP/247713/2012.
13. Sandoz, a Novartis division. Development of biosimilars [cited 2019 Mar 01]. Available from: https://www.sandoz.com/our-work/biopharmaceuticals/development-biosimilars.

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