Biosimilar medicines —
a commitment to scientific excellence

With biosimilar medicines, patients and healthcare providers benefit from high quality and efficacious therapeutic alternatives.

But how are biosimilar medicines developed, and how is their efficacy and safety ensured?
Biological medicines display an inherent degree of minor variability (microheterogeneity), which is tightly controlled\(^1\)

Biological medicines are made in living organisms and purified through complex manufacturing processes\(^2\)

Biological medicines consist of relatively large and often highly complex molecular entities\(^3\)

Any biological medicine will display microheterogeneity, even between different batches of the same product. This normal feature is tightly controlled\(^3\)

The heterogeneity of biological medicines not only reflects the natural variation of these molecules, but also the variability of the production process\(^1,3\)

Throughout their lifecycle, biological medicines undergo changes to their manufacturing process\(^1,2\)

Changes in the manufacturing process of a biological medicine are very common and can include:\(^3\)

- Upscaling the process
- Yield improvement
- New purification methods
- Change of cell line
- Change of manufacturing site

Following any change, comparability testing must be performed to ensure that the safety and efficacy is maintained across the different versions of the same biological medicine\(^4\)

The acceptable variability of the reference biological medicine over its lifecycle designates the goalposts for biosimilar product development\(^5,6\)

**Number of approved manufacturing changes for monoclonal antibodies according to risk category**

- High risk
- Moderate risk
- Low risk

**Figure adapted from Vezér et al. 2016\(^2\)**

**References:**
Changes to manufacturing of biological medicines are approved following a stepwise comparability exercise\(^1\)

Comparability bridging studies and adherence to specific pharmacovigilance regulations may be required, depending on the nature of the changes made to the manufacturing process\(^2\)

- Originator manufacturers rely almost exclusively on analytics and extrapolation of indications to obtain approval for the process changes\(^3,4\)

- Regulators have over two decades of experience in evaluating and approving these changes, based on comparability exercises in line with internationally agreed standards\(^5\)

- When comparability has been demonstrated, the new version of the product can be introduced to the market without informing prescribers, pharmacists, or patients\(^6\)

The scientific principles for establishing biosimilarity are the same as those for demonstrating comparability after a change in the manufacturing process of an already licensed biological medicine\(^7,8\)

Biosimilar medicine development is target-orientated, comparative, and follows a stepwise approach\textsuperscript{1–3}

1. Define and characterize the reference product

The sensitivity of \textit{in vitro} characterization continues to improve, and has increased 10 million-fold between 1990 and 2011 for some methods\textsuperscript{4}

2. Complete manufacturing process development of the biosimilar medicine

Biosimilar medicine process development is a reiterative procedure whereby the product quality is continuously reviewed\textsuperscript{1,2}

3. Confirm comparability between the biosimilar medicine and the reference product

The quality, non-clinical, pharmacokinetics (PK)/pharmacodynamics (PD), and clinical profiles of the biosimilar are sequentially compared with the reference product\textsuperscript{1,2}

The range of variability allowed for a biosimilar medicine is the same as that allowed between batches of the reference medicine\textsuperscript{1–3}

Example of variability between a biosimilar and the reference medicine

- Variability (yellow shadow) between a biosimilar and the reference medicine is comparable to what may occur between different batches of the same biological medicine.

- Minor variability, e.g. in glycosylation (represented by small blue triangles) may be allowed, while the protein’s amino acid sequence (circles) and biological activity are the same.
Quality comparability establishes highly similar physiochemical properties and biological activity\(^1,2\)

- Analytical and functional comparability studies are the foundation of biosimilar medicine development\(^1,2\)

- Analytical testing is a more sensitive means of detecting differences than randomized clinical trials\(^1,2\)

- The biosimilar medicine and the reference product must be highly similar at a molecular level\(^1,3\)
  - The primary structures (amino acid sequences) must be identical
  - Higher-level structures must be indistinguishable

- Impurities, biological activity, and post-translational modifications are also compared\(^1,2\)

- The degree of quality similarity will determine the scope and the breadth of the required non-clinical and clinical data to rule out differences in clinical performance\(^1,2\)

Non-clinical comparability establishes that functionally, the biosimilar medicine and the reference product are similar\textsuperscript{1,2}

- The biosimilar medicine must display highly similar functionality to the reference biological medicine.
- Multiple \textit{in vitro} (and in exceptional cases, \textit{in vivo}) assays are used to measure the binding of the biosimilar medicine to target antigens or receptors.

PK/PD comparability establishes that the biodistribution of the biosimilar and the reference product are similar

- Comparative pharmacokinetic (PK) and/or pharmacodynamic (PD) studies in humans are designed to further support comparability data, or to detect potential differences between the biosimilar medicine and the reference product\(^1\)

- The PK study is a major gatekeeper in the clinical biosimilarity exercise

- In certain cases, the comparative analytical, non-clinical, and human PK/PD (clinical immunogenicity) studies may be sufficient to definitively confirm biosimilarity to the reference product\(^1,2\)

Clinical comparability complements and confirms the comparability demonstrated at the previous steps

- Tailored clinical comparability, where appropriate, confirms that the structural concordance translates into clinical performance, and is designed to rule out clinically relevant differences in safety or efficacy¹

- Comparative clinical trials, where needed, are performed in a scientifically justified ‘clinical model’ that is sensitive to small differences²–⁶

- Clinical safety (including immunogenicity) is important throughout the clinical development program. Safety data is captured during the initial pharmacokinetic (PK) and/or pharmacodynamic (PD) studies, and the comparative clinical study, where required²–⁶

The biosimilar medicine is only approved if there are no clinically meaningful differences from the reference product⁷

How can we tailor biosimilar development?

- Continuously apply evolving regulatory sciences;
- Maintain robust regulatory standards that have resulted in an impeccable track record of biosimilar medicines;
- Adapting the biosimilar framework with the latest knowledge is reflected in objectives of EMA, MHRA, WHO

  • e.g. EMA objective: “Further develop the biosimilar framework, adapting the clinical part of the development to the latest scientific knowledge concerning the comparability assessment”
  
  • MHRA Objective: “Develop and publish guidance on a new innovative UK licensing procedure for biosimilar products to operate from 1 January 2021 to reduce the burden on clinical trial data generation”

3. WHO - Main outcomes of the meeting of the WHO Expert Committee on Biological Standardization held from 21 to 25 October 2019, accessed 21 April 2020; see also Backup-slide “WHO Discussion)
# Evolution of biosimilar development options for therapeutic proteins

## 5 step approach

1. Physicochemical analysis
2. Functional analysis
3. Non-clinical (in-vivo) 
   - An *in vivo* animal study is usually not considered necessary
4. Clinical PK/PD
5. Comparative clinical efficacy

## 4 step approach

1. Physicochemical analysis
2. Functional analysis
3. Clinical PK
4. Comparative clinical efficacy or, instead clinical PD with sufficiently qualified PD marker

## 3 step approach

1. Physicochemical analysis
2. Functional analysis
3. Clinical PK (Additional confirmation of immunogenicity/safety only if needed)

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*No PD as early measure of physiological response required for clinical efficacy*
Current resources

An Efficient Development Paradigm for Biosimilars

Christopher J. Webster, Ann C. Wong & Gillian R. Woollatt

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Abstract

The current development paradigm for biosimilars required by regulators in highly regulated jurisdictions is derived from the development of novel drugs and is unnecessarily burdensome and inefficient. It requires the accumulation of data from analytical, nonclinical (including in vivo studies in some jurisdictions), and clinical studies (including powered efficacy studies in most cases); this paradigm is known as "totality of evidence" (ToE) and does not admit a conclusion of biosimilarity from analytical data alone. The record of biosimilar approvals in these jurisdictions shows that no biosimilar candidate that has been found highly similar to its reference in analytical and pharmacokinetic studies has failed to be approved. We propose a new paradigm ("confirmation of sufficient likeness", CSL) that emphasizes the demonstration of analytical resemblance between the biosimilar candidate and its reference, and permits the conclusion of biosimilarity upon this basis. CSL does not entail bridging studies between reference products, in vivo nonclinical studies, or powered efficacy studies and is, therefore, substantially more efficient than ToE while maintaining equivalent scientific rigor. Such efficiency will contribute to the attractiveness as well as the sustainability of biosimilars as a therapeutic modality.

Evolution of the EU Biosimilar Framework: Past and Future


Abstract

The approval of biosimilars in the EU follows a comprehensive scientific assessment based on stringent regulatory standards. While the initial approach to biosimilars was understood, cautious, and focused on the risk of uncontrolled changes in the molecule to protect patients safety, the scientific and clinical progress and accumulated experience with biosimilars continues to shape regulatory requirements, potentially leading to a refined balance of clinical trials. This trend is expected to continue, for example, by increasing regulatory pharmacokinetic evaluation and biosimilarity, but novel steps remain to enable this progress, especially for complex molecules with several or even mechanisms of action. A review of the available guidance and ongoing public engagement regarding biosimilar approval is due in the near future. This review focuses on the nature and extent of clinical evaluations of biosimilarity considered necessary in addition to analytical and nonclinical data. Changes resulting from the results of future non-clinical comparability exercises are discussed, with the aim of identifying whether certain elements of the comparability exercise are more important than others in determining biosimilarity. This includes analytical and pharmacokinetic comparison, the organization of the biosimilar development in addition, pharmacokinetic similarity is an indispensable prerequisite for any biosimilar approval, or could planning on behalf of the sponsor in order to address potential future issues for each, for example, because of potential drug-drug interactions, underestimated test design or other methodological issues. Comparative pharmacokinetic studies are a standard requirement for biosimilar development and are usually more efficient and more economical than clinical efficacy studies. Missing endpoint-related differences may explain why a demonstration of equivalent efficacy would not require a finding of biosimilar pharmacokinetic profiles in vivo as in the case of molecular impairment. However, the necessity of efficacy studies differs depending on the proposed pharmacological action of the biological drug in vivo, in which case both types of studies differ. Efficacy studies should ideally be designed as experience trials to ensure that the efficacy of the biosimilar is neither decreased nor increased compared to the reference product. However, assuming uncertainty regarding generally increased efficacy of the biosimilar may not be acceptable in exceptional cases, provided that the data from other mechanisms of action are not only supported by a combination of nonclinical studies and clinical trials. In contrast, uncertainty regarding potential inferiority of the biosimilar may not be acceptable at all. We conclude that the EU biosimilar regulatory framework is robust and able to adapt to advancing knowledge and expanding and to strike a balance between regulatory standards, patient safety and affordability of biosimilars.

The Path Towards a Tailored Clinical Biosimilar Development

Martin Szanyi, Szabolcs Barczay, Peter Szpena, Gulyas János, Kádár Kristóf, Németh Péter, Szanyi Márton, László Marosi-Kalmár

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Abstract

Since the first approval of a biosimilar medicinal product in 2006, scientific understanding of the features and development of biosimilar medicines has accumulated. This review scrutinizes public information on development programs and the contribution of the clinical studies for biosimilar approval in the European Union (EU) and the United States (US) until November 2009. The retrospective evaluation of the programs that eventually obtained marketing authorization and/or licenses revealed that in 95% (36 out of 38) of all programs, the comparative clinical efficacy studies confirmed similarity. In the remaining 5% (2 out of 38), despite meeting efficacy outcomes, the biosimilar candidates exhibited clinical differences in immunogenicity that required changes to the manufacturing process and additional clinical studies to enable biosimilar approval. Both instances of clinical differences in immunogenicity occurred prior to 2010, and the occurrence of these cases is unlikely today due to state-of-the-art assays and improved control of process-related impurities. Biosimilar candidates that were not approved in the EU nor in the US were not approved due to reasons other than clinical confirmation of efficacy. This review of the development history of biosimilars allows the proposal of a more efficient and expedited biosimilar development without the routine need for comparative clinical efficacy and/or pharmacodynamic studies and without any compromise in quality, safety, or efficacy. This proposal is scientifically valid, consistent with regulation of all biologics, and maintains robust regulatory standards in the assessment of biosimilar candidates. Note: The findings and conclusion of this paper are limited to biosimilar products developed against the regulatory standards in the EU and the US.
Approval of all indications of biosimilar medicines is based on the totality of evidence

- A biosimilar may be approved for one or more indications for which its reference product is licensed, but for which there was no head-to-head clinical comparison
- These indications are individually evaluated based on sound science
- The approvals are based on extrapolation of data, which is an established regulatory and scientific principle. This approach is also used by regulators in the approval of changes to the reference product manufacturing process, and in pharmaceutical development of all biological medicines

While no one piece of information is sufficient to demonstrate biosimilarity, when taken together, the evidence forms a comprehensive picture in each and every approved condition

Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise. Extrapolation of indications is based on the clinical experience with the reference product and the entire similarity exercise.

Abbreviations: PK, pharmacokinetic; PD, pharmacodynamic


Figure adapted from Windisch J.
Biosimilar medicine development requires significant investment and state-of-the-art technologies

- **Significant investment**, costing 100–300 million USD and taking up to eight years to develop, is needed to achieve a successful similarity exercise.¹

- **Highly sophisticated analytical tools** allow for a detailed characterization of the biosimilar medicine and the reference product³,⁴

- Due to technological advances, biosimilar medicines are usually better characterized than their reference products, which were characterized at the time of their initial approval 10 or 20 years earlier⁵,⁶

- Biosimilar medicines are manufactured, distributed, and monitored according to the same standards as other medicines, and regulatory authorities perform periodic inspections of the manufacturing sites.²

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Patients and healthcare providers can trust biosimilar medicines, as they are approved according to the same high standards and by the same regulators as all other medicines.

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Summary: Biosimilar medicines — a commitment to scientific excellence

- **Biological medicines display an inherent degree of minor variability**, which is tightly controlled\(^1\)
- Throughout their lifecycle, biological medicines undergo manufacturing changes\(^2\)
- **Tailored clinical comparability**, where appropriate, complements and confirms the comparability demonstrated at the previous steps
- Scientific principles for establishing biosimilarity are the same as those for demonstrating comparability\(^4\)

**Stepwise comparability exercises** ensure there are no clinically meaningful differences between the biosimilar and the reference product\(^5,6\)

Development of biosimilars requires significant investment and state-of-the-art technologies\(^4\)

WHO, EMA/EU, FDA/USA, HC/Canada, PMDA/Japan, TGA/Australia and others, all require extensive evidence that a biosimilar is highly similar to a reference product, and that there are no meaningful differences\(^7,8\)