BIOSIMILAR REGULATION IN THE EUROPEAN UNION

Attitude, Skills, and Knowledge in Oncology Biosimilars

This document summarises the regulatory guidance on biosimilar medications in the European Union and European Economic Area. It is intended as a concise summary of the key guidance for biosimilar use across the EU and EEA, available to download and share with your multidisciplinary team. It is part of a learning programme that provides material covering Canada, the EU, Japan and the United Kingdom. More information and additional resources can be found at: **https://ask-biosimilars.com/**.

1 Introduction

Regulated by: The European Medicines Agency (EMA)

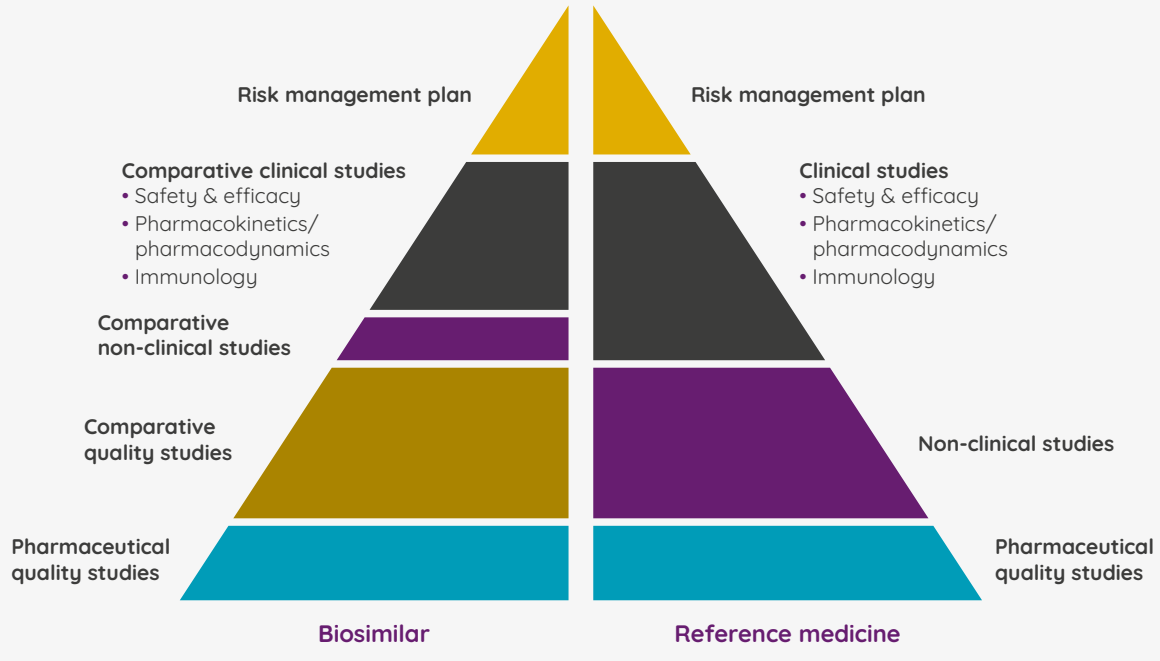
Definition of a biosimilar: A biological medicine highly similar to another already approved biological medicine in the EU and EEA for which marketing exclusivity rights have expired.

Approval process: Demonstration of similarity to the reference medicinal product, in terms of quality characteristics, biological activity, safety and efficacy.[1]

The traditional approach used with generics is not sufficient to permit approval of biosimilars. Approval of a biosimilar is based on a comprehensive comparability programme designed to generate evidence of similarity with a reference product. Data requirements for approval of a biosimilar build on existing knowledge of the reference product, specifically published literature if the reference product is not the property of the company developing the biosimilar. It is not generally expected that the entire clinical development programme be repeated.

Reference product requirements: The same reference product should be used throughout and should be a medicinal product authorised in the EU or EEA. Reference products not authorised in the EU or EEA can be used with caution, provided they have been authorised by a regulatory authority with similar scientific and regulatory standards as the EMA and are a similar formulation.

Comparison of data requirements for approval of a biosimilar vs reference medicine – adapted from EMA 2019.[2]



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2 Comparability

Guiding principle: Demonstration of comparability to the reference product in terms of quality characteristics, biological activity, safety and efficacy.

Extent of data required to demonstrate biosimilarity is dependent on the nature and complexity of the reference product. Factors taken into consideration include mode of action of active substance, pathogenic mechanisms involved in one or many relevant indications, immunogenicity and availability of suitable biomarkers. The safety profile of the reference product will also direct the design of studies.[3]

EMA recommended approach: Separate guidelines are issued by the EMA according to the nature of the molecule.[4] Comparability assessed according to three domains.

1. Quality: analytical and functional
2. Non-clinical: pharmaco-toxicological
3. Clinical: pharmacokinetic, pharmacodynamic, efficacy, safety (including immunogenicity) and pharmacovigilance (risk management)

Quality profile of biosimilars: Physicochemical and biological similarity between the reference product and the biosimilar must be proved. Assessment of:[2]

- structural and other physicochemical properties
- purity (traces of residues from the manufacturing process have to be controlled and must not exceed acceptable levels)
- biological activity
- excipients and starting materials
- strength and formulation
- control of the manufacturing process (to ensure that the active substance and finished product conform with the accepted ranges for technical specifications)
- stability of the active substance and finished product during shelf-life under defined storage.

Non-clinical studies: Stepwise approach recommended. Studies should:

- prove observed differences in quality attributes are not clinically relevant
- compare the concentration–activity/binding relationship of the biosimilar and the reference medicinal product.

Biotechnology-derived proteins may mediate *in vivo* effects that cannot be fully elucidated by *in vitro* studies. *In vivo* studies may be used to compare pharmacokinetics, pharmacodynamics, safety or immunogenicity of the biosimilar to the reference product if the *in vitro* studies raise any concerns, e.g., insufficiently characterised glycosylation.

2.1 Confirmatory pharmacokinetic trial

Pharmacokinetic studies are an essential part of the clinical comparability exercise.

Purpose: To exclude any relevant pharmacokinetic differences that could indicate presence of structural and/or functional differences that could impact the efficacy, safety or immunogenicity of the product.

Design: It is important to use an adequate sample size to ensure the statistical analysis produces meaningful results.

Crossover design preferred – more sensitive to detect differences

- Parallel group design may be necessary for substances with a long half-life and/or a high risk of immunogenicity.

Studies in healthy volunteers

- Single-dose crossover studies preferred to fully characterise the pharmacokinetics, including the late elimination phase.

Anti-drug antibodies should be measured using appropriate sampling time points.

Results: Key pharmacokinetic parameters defined at study design, may be similar to that of conventional bioequivalence studies.

- Interpretation of results more stringent than standard generic bioequivalence studies.

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Pharmacodynamic markers:

- Selected based on relevance to the clinical outcome
- Added to the pharmacokinetic studies whenever feasible

Under certain circumstances, comparative pharmacokinetic/pharmacodynamic studies may be sufficient to demonstrate clinical comparability of biosimilar and reference product.

1. Pharmacodynamic marker is an accepted surrogate efficacy marker and can be related to patient outcome
2. Pharmacodynamic marker is relevant to the pharmacological action of the active substance and a clear dose–response or concentration–response relationship has been demonstrated
3. In exceptional cases, if physicochemical, structural and *in vitro* biological analyses and human pharmacokinetic studies with a combination of pharmacodynamic markers that reflect the pharmacological action and concentration of the active substance provide robust evidence for biosimilar comparability.

2.2 Efficacy trials

Requirements: Demonstrate comparable clinical equivalence of biosimilar and reference product

- At least one adequately powered, randomised, parallel group, double-blind, comparative clinical trial
  - Appropriate efficacy endpoints in a population that represents the approved therapeutic indication(s) of the reference product
- Approval is intended to build on existing knowledge of the reference product gained during its clinical use
  - Reference medicine's clinical development programme does not need to be repeated
  - Product-specific guidance directs the extent of data requirements
- Equivalence margins set for the specific indication and depend on endpoints
  - Should represent the largest difference in efficacy that would not matter in clinical practice.

2.3 Safety

Requirements: Data are collected during all clinical and non-clinical studies. Since the manufacturing process for the biosimilar will be different to that of the reference product, the capture of any possible safety concerns that may result, especially those related to infusion-related reactions and immunogenicity, are of particular importance.

Immunogenicity: The potential for immunogenicity should be investigated in a comparative manner via analytical assay (*in vitro* or *ex vivo*) for antibodies against the biosimilar and the reference molecule to measure the immune response to both molecules.

When evaluating anti-drug antibodies, it is important to consider:

- duration
- incidence
- activity (e.g., cross-reactivity, target epitopes and neutralising activity)

Interpretation in relation to the potential effect on clinical efficacy and safety parameters. Analyses should show that immune responses do not alter the biosimilar's efficacy.

The potential for immunogenicity may be increased or decreased for the biosimilar compared with the reference product, and it is recommended to pre-specify an additional exploratory subgroup analysis of efficacy and safety in those patients that did not mount an anti-drug antibody response during the clinical trial.

2.4 Pharmacovigilance

Pre-authorisation clinical studies are limited

- Usually insufficient to identify rare adverse effects
- E.g., immunogenicity

Manufacturers are also requested to implement a pharmacovigilance system and risk manaement plan

- Risk management plan for a biosimilar must reflect that of the reference product in terms of:
  - safety concerns
  - additional pharmacovigilance activities
  - additional risk minimisation
- The risk management plan must also include any new safety concerns detected for the biosimilar candidate, as these are unlikely to be due to the active molecule, but rather factors such as excipient or device

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The risk management plan should take into account identified and potential risks associated with the use of the reference product, describing how these issues will be addressed in post-marketing follow-up, including monitoring of immunogenicity. Existing risk minimisation activities for the reference product should be included into the risk management programme of the biosimilar.

The risk management plan should be well organised and allow full access to the data.

Traceability: Appropriate measures should be taken to enable identification of a specific product that is the subject of a suspected adverse reaction report (e.g., brand name and batch number).

2.5 Extrapolation from one therapeutic indication to another

When biosimilarity is demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable. While extrapolation of indications was an area where, initially, there was hesitation in the large-scale implementation of biosimilars in hospital formularies, it is now more widely accepted.

Extrapolation should be considered in the light of the totality of data, i.e., quality, non-clinical and clinical data.
If biosimilar comparability has been demonstrated by thorough physicochemical and structural analyses as well as by *in vitro* functional tests complemented with clinical data (efficacy and safety and/or PK/PD data) in one therapeutic indication, extrapolation is possible.[5]

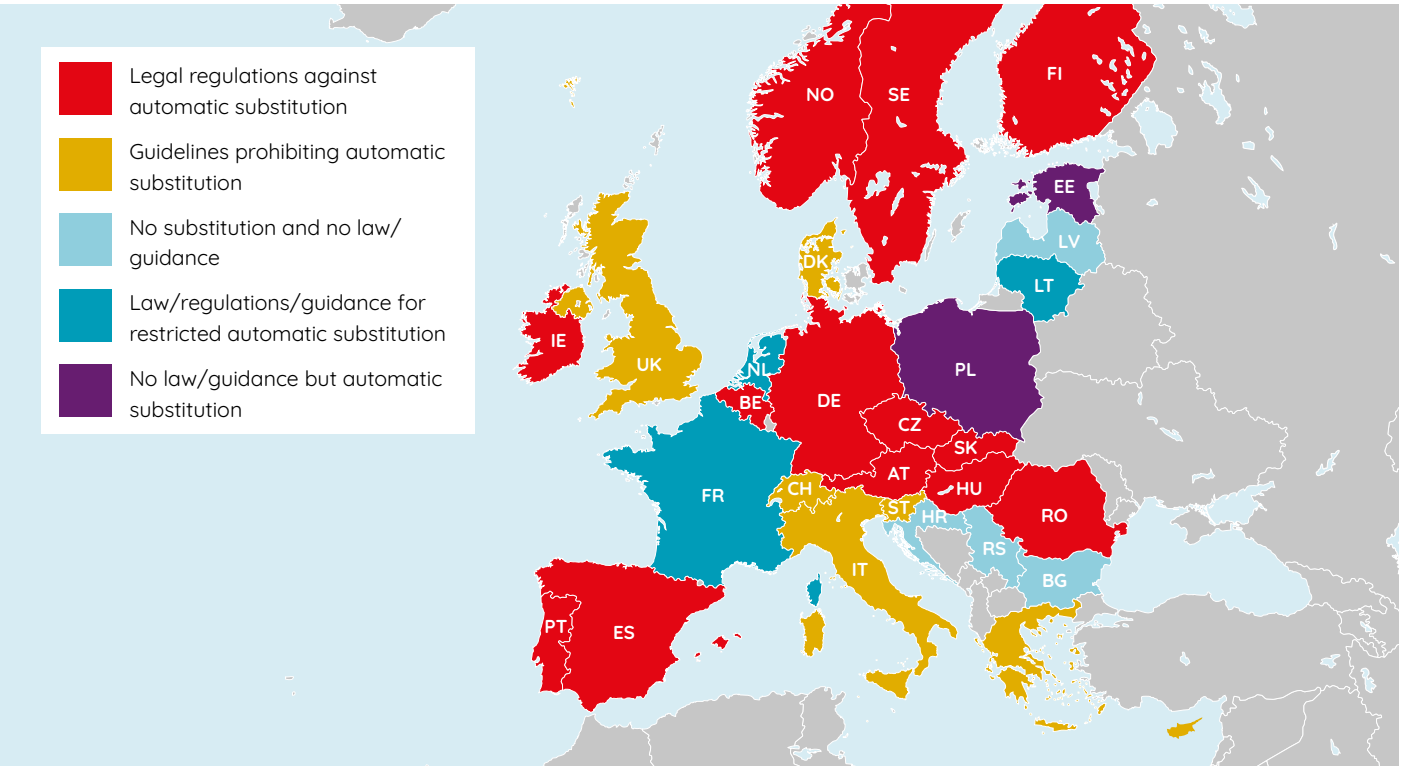
However, additional data are required in certain situations.

- Active substance of the reference product interacts with receptors that may have a different impact in untested therapeutic indications
- Active substance has more than one active site, which may have a different impact in different therapeutic indications
- Studied therapeutic indication is not relevant to the others in terms of efficacy or safety.

3 Interchangeability

Regulations relating to the interchangeability of biosimilars and biologics varies by region.

- Decisions about interchangeability are made at the national level within the EU and EEA – processes can vary within countries
  - This creates a lack of consistency within Europe in terms of the same drug being administered to similar patients under different rules
- Most member states do not allow automatic substitution
  - Many have introduced rules to avoid automatic substitution
  - Some allow limited substitution. E.g., in Germany, regulations vary between ambulatory and hospital care
  - **It is important to refer to local policies.**



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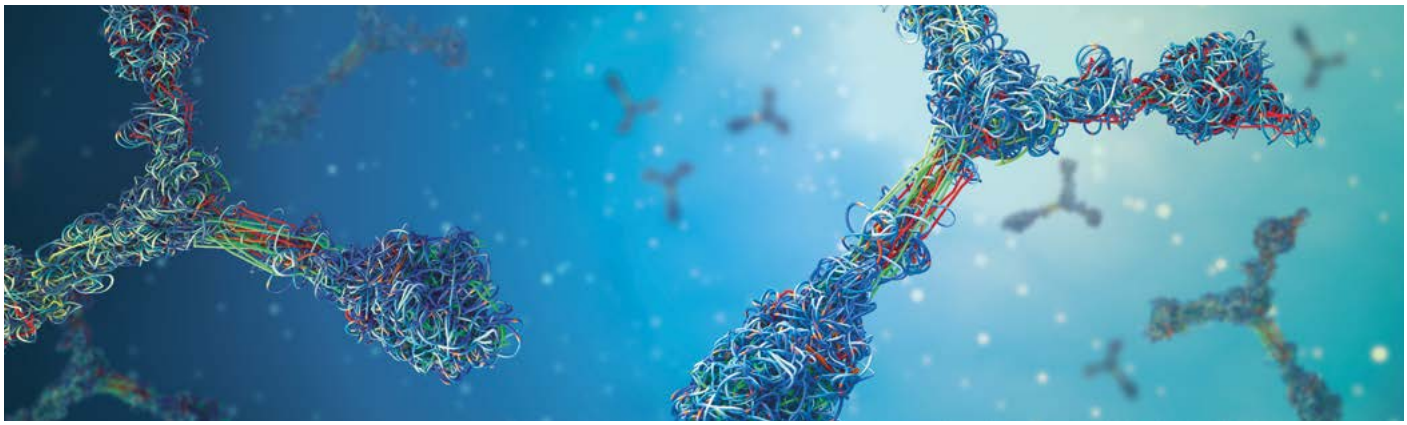

4 Manufacturing

Biosimilar manufacturers generally will not have access to all information that allows precise replication of reference products

- Novel manufacturing processes may introduce changes not present in the reference product:
  - molecular modifications (e.g., glycosylation)
  - product-related substances (e.g., isoforms)
  - impurities

Differences from the reference product may have undesired consequences (e.g., atypical glycosylation) that influences the structure of the molecule

- Differences in expression
- Different excipients used for stability
- Changes in containers used for storage

Guiding regulations: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and Committee for Medicinal Products for Human Use (CHMP) quality guidelines.[5,6]

Comparability assessment during manufacturing: Should demonstrate that changes (e.g., to the excipients or purity profile) during development do not give rise to any concerns or affect quality, safety or efficacy compared with the reference product. Any observed differences must be justified with regard to their potential impact on safety and efficacy. Amino acid sequences are expected to be the same, other than justified post-translational modifications.

Differences that have a potential impact should be reduced and stability limits for critical quality attributes (i.e., key physical, chemical, biological or microbiological properties that ensure product quality) should be set to prevent drift over time.

Changes to manufacturing process: Changes during development require a comparability assessment.[7] If a manufacturing change takes place after comparability trial(s) or approval, a more thorough comparability exercise is generally required, including repetition and validation of some or all of the studies. If this comparability exercise cannot rule out a significant impact on the non-clinical attributes and on the efficacy and safety profile of the drug, additional clinical studies may have to be performed.[8]

Manufacturers often implement changes to the manufacturing processes of products, e.g., to increase scale or improve product stability. Following approval of a biologic drug, changes made to the manufacturing process generally require demonstration that the changes did not adversely impact the safety and efficacy of the biologic.

Posology (dose and frequency of dosing) and route of administration

- Must be the same as the reference product
  - Deviations in the strength, pharmaceutical form, formulation, excipients or presentation are possible if justification and relevant data are provided. In practice this is complicated and uncommon.

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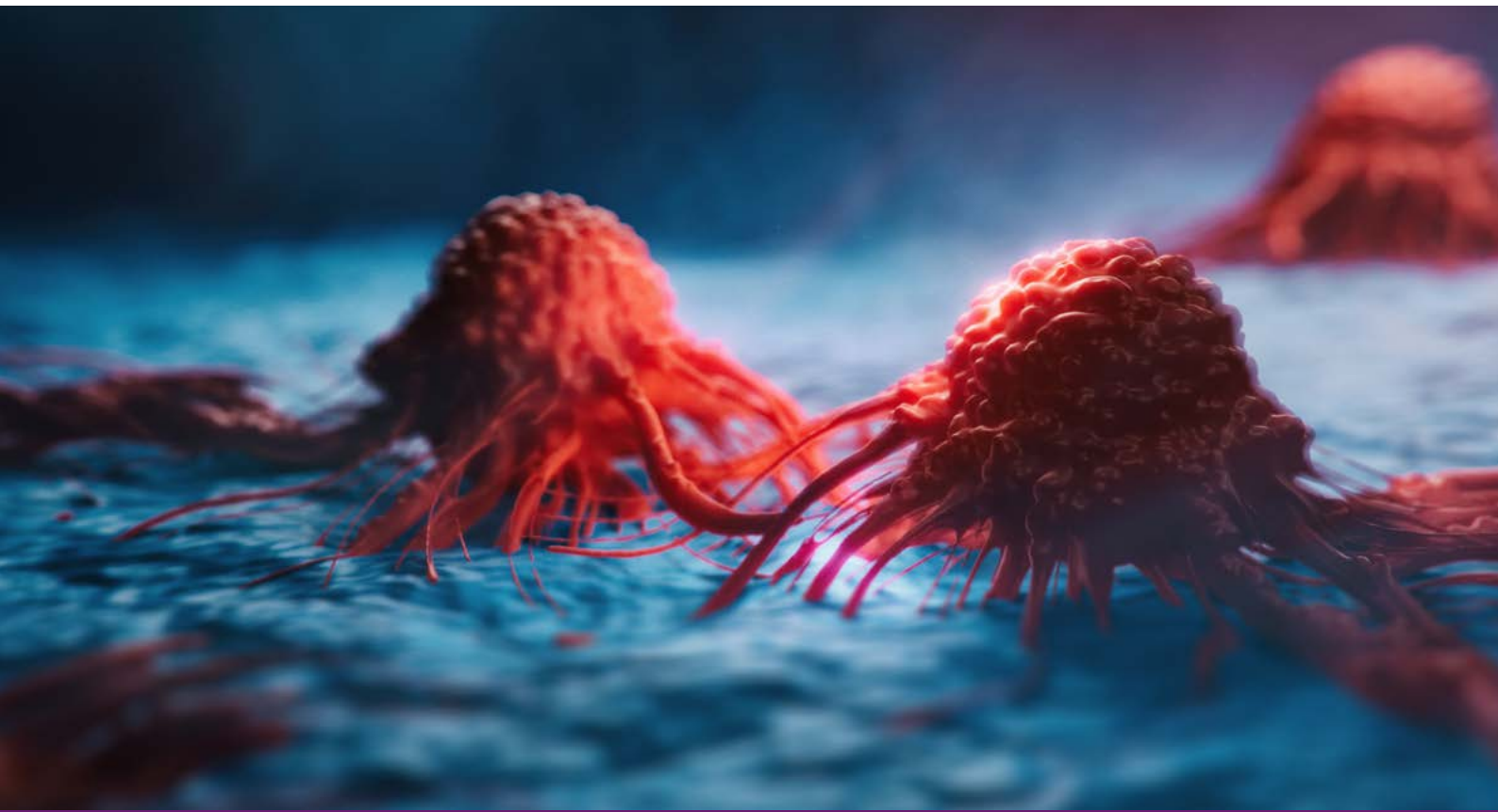

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