BIOSIMILAR REGULATION IN THE UNITED KINGDOM

Attitude, Skills, and Knowledge in Oncology Biosimilars

This document summarises the national regulatory guidance on biosimilar medications in the United Kingdom. It is intended as a concise summary of the key guidance for biosimilar regulation and approval, 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 Medicines and Healthcare products Regulatory Agency (MHRA)

- Guidance aligns closely with that of the European Medicines Agency (EMA), with some notable differences.
- Northern Ireland follows the EU acquis for biosimilar approval, and the MHRA regulates these applications accordingly

Definition of a biosimilar: A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine'). Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines.[1]

Approval process: Great Britain (i.e., Scotland, England and Wales) follows the principles of the EMA and is based on a comprehensive comparability programme designed to generate evidence of similarity with the reference product.

Similarity must be established in terms of physicochemical properties, biological activity/potency and clinical profiles.

Reference product requirements: The same reference product must be used throughout the comparability programme and should ideally include a product licensed in the UK. A reference product that is not approved in Great Britain can be used but should be authorised in and sourced from a country with similar scientific and regulatory standards as the UK.[2]

The reference product must have been authorised for at least 8 years for approval and have 2 years of market data.

2 Comparability

Guiding principle: Establishment of comparability between the biosimilar and reference product, ensuring that previously proven safety and efficacy of reference product also applies to the biosimilar.

Recommended approach: The MHRA recommend stepwise approach is to ask for evidence of:

- Extensive physicochemical and biological characterisation
- Pivotal comparative pharmacokinetic studies
- Potential comparative efficacy studies
- Unlike under EMA guidance, an efficacy study is not mandatory

Quality profile of biosimilar: proven to be comparable to the reference product. Assessment should

- Include comprehensive analyses
- Use state-of-the-art methods (e.g., liquid chromatography tandem mass spectrometry [LC-MS-MS])
- Have suitable sensitivity to determine similarities and potential differences in quality attributes and potential impacts on safety (including immunogenicity) and efficacy

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.

Relevant guidance: In addition to MHRA guidance, the EMA guideline on similar biological medicinal products[3] should be consulted for granular detail.

Comparative *in vitro* studies: The MHRA assess *in vitro* studies alongside the related quality data in the biosimilar comparability evaluation. Distinct from EMA guidance, *in vivo* studies are not requested.

2.1 Confirmatory pharmacokinetic trial

Clinical comparability exercises should always include a pivotal comparative pharmacokinetic trial, which may include the measurement of pharmacodynamic markers, if available.

Purpose: To demonstrate equivalence to the reference product, ideally in healthy volunteers

Design: Crossover design preferred – more sensitive for detecting differences

- May not be suitable for reference product with a long half-life or notable immune response

Studies in healthy volunteers

- Single-dose studies in healthy volunteers may use lower doses than therapeutic doses
- May not be feasible
  - Profile can be studied in patients as part of a multiple-dose study

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Results: Demonstration of equivalence of the primary pharmacokinetic parameters, usually peak and overall exposure (C_{max} and AUC)

- **Equivalence interval of 80–125% acceptable**

Collection and reporting of safety and immunogenicity data:

- Injection-site or infusion-related reactions
- Anti-drug antibody rate and kinetics
  - Assessment of impact of such reactions on the pharmacokinetics (and pharmacodynamics, if applicable) through prespecified group analysis of ADA-negative and ADA-positive subjects

2.2 Efficacy and safety trials

Requirements: Confirmatory efficacy trials may not be required by the MHRA for approval if scientific rationale supports the approach.

- Requires a robust, well-argued justification discussing comparable efficacy that can be assumed from comparable binding properties and functional characteristics, and the assumption that any observed differences are not clinically relevant, based on specific experiments and available literature
- Intended to streamline the approval of biosimilars and supported by the 2020 blueprint for a biosimilar pathway4
  - In-depth knowledge of reference product and high-performing analytical tools largely predict clinical comparability, subject to confirmation by a comparative pharmacokinetic trial[4]
- This approach differs from EMA guidance, which only allows omission of efficacy studies in exceptional cases

Immunogenicity: Risk-based assessment of immunogenicity of biosimilar, potential rates of binding or neutralising anti-drug antibodies and their clinical relevance are informed by extensive clinical experience with the reference product.

- Justification for comparability of the biosimilar is not informed by whether the immunogenicity and safety risks are low or high
- Quality attributes, including protein aggregates, impurities and formulation of the biosimilar used as the basis for justification that safety and immunogenicity are comparable to those of the reference product
- Safety and immunogenicity data should also be collected during the confirmatory pharmacokinetic trial

Comparative efficacy and safety trials are requested where there is a lack of understanding of the biological functions of the reference product related to its clinical effects, or where the relevant critical quality attributes may not be sufficiently characterised.

Additional clinical safety data may be required where safety uncertainties cannot be resolved without patient exposure pre-licensing, e.g., where serious adverse drug reactions to the reference product have unpredictable root causes.

2.3 Extrapolation from one therapeutic indication to another

Once a biosimilar has been shown to be highly similar to the reference product in terms of analytical characteristics and functional properties it can be approved for all indications for which the reference product is licensed (provided they are not protected by market exclusivity or patent), without being evaluated in each disease scenario. **This is distinct from requirements of other regulatory authorities, who may request additional data if the biosimilar's mechanism of action underlying its efficacy in different indications is complex.**

This process is called extrapolation and is intended to avoid conducting unnecessary clinical studies.

The scientific justification for the extrapolation of indications depends on detailed knowledge of:

- Mechanism of action
- Molecular targets
- Pharmacokinetic and pharmacodynamic profiles
- Immunogenicity
- Adverse events

2.4 Pharmacovigilance

Biosimilars are subject to additional monitoring after marketing authorisation and the product information carries a black inverted triangle (▼).

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 management 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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Any ongoing additional pharmacovigilance activities for the reference product also apply to the biosimilar candidate

- Recommended to be via collaboration or participation in studies or registries already in place for the reference product
  - Enables collection of real-world information to support characterisation of risks and signal detection of potential safety signals related to the reference product and its biosimilars

A key requirement of healthcare providers is to ensure continuous product and batch traceability in clinical use to support detection of any important safety issues that may be product- or batch-specific

Nomenclature: Use of the invented brand name

- Allows newly emerged and potential product-specific safety concerns to be rapidly identified and evaluated
- Allows product to be traceable to location and patients
- Distinct from the EMA use of International Non-proprietary Name (INN) followed by name of the marketing authorisation holder

Traceability: Accurate traceability of biosimilars by brand name and batch number must be assured in the post-marketing setting

- Training must be provided to healthcare professionals to support reporting of brand name and batch number when reporting adverse reactions
- Should be fully integrated in the healthcare settings, e.g., electronic data recording and record linkage
- Additional risk minimisation measures required for the reference product should also be implemented for the biosimilar candidate, e.g., educational materials for healthcare professionals and patients, or patient alert cards

3 Interchangeability

The definition of 'interchangeability' differs between regulatory agencies. Once authorised, a biosimilar product is considered interchangeable with its reference product

- Switching patients from one product to another has become routine clinical practice
- Official guidelines state that **substitution at the pharmacy level without consulting the prescriber is not permitted**[5]
  - Decisions at the pharmacy level rarely occur in practice:
    - Decisions are often made at the institutional level by a central drugs and therapeutics committee
    - A switchover strategy will be created in collaboration with relevant healthcare practitioners and patients will be informed of the switch

European Association of Hospital Pharmacists (EAHP) position on interchangeability, substitution and switching[6]

- A reference product and its biosimilar(s) are interchangeable and can be switched
- A biosimilar product and other biosimilar(s) to the same reference product are interchangeable and can be switched
- Decisions regarding switching and substitution should involve the relevant stakeholders (e.g., patients, prescribers and pharmacists)
- Decisions may be made at the national level, involving the relevant stakeholders
- Under certain conditions, substitution at the hospital pharmacy level can occur

4 Manufacturing

Importance of manufacturing process: Must be well-defined to ensure the biologic is produced on a consistent basis.[7]

Challenging for biologic manufacturers:

- Living systems are used in production
- Inevitable batch-to-batch variation[8]
  - within manufacture of reference biologics
  - within manufacture of each biosimilar

Comparability assessment: 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 in manufacturing process from reference product: Biosimilar manufacturers generally will not have access to all information that allows precise replication of reference products. Novel manufacturing processes may introduce differences from 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 influence the structure of the molecule

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

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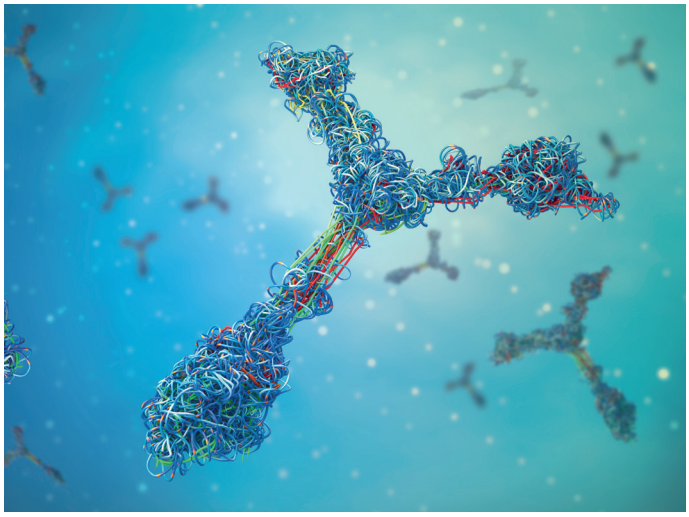
The impact of these changes should not significantly affect quality, efficacy, or safety of the biosimilar.

Changes to manufacturing process: 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



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