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Guidance

Guidance on the licensing of biosimilar products

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1. Introduction

The purpose of this guideline is to provide developers of similar biological medicinal products (also known as biosimilars) with a clear outline of the requirements for biosimilar products in Northern Ireland/Great Britain/UK.

Applicants should also take into account principles contained within the Committee for Medicinal Products for Human Use (CHMP) guidelines:

- Guideline on similar biological medicinal products
(https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-rev1_en.pdf)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues
(https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues
(https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf)
- Guideline on immunogenicity assessment of therapeutic proteins
(https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-immunogenicity-assessment-therapeutic-proteins-revision-1_en.pdf)
- relevant product-specific biosimilar guidelines (<https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/multidisciplinary/multidisciplinary-biosimilar>)

This MHRA guidance contains further clarifications and some revisions to these CHMP guidance documents, which take into account the scientific and regulatory experience gained since the first biosimilar product was licensed in 2006, including biosimilar monoclonal antibodies and fusion proteins licenced from 2013
(<https://www.sciencedirect.com/science/article/pii/S1359644620303433?via%3Dihub>).

Clarification about this guidance can be sought by sending an email to the Regulatory Information Service at MHRA in the first instance: RIS.NA@mhra.gov.uk; or by seeking MHRA scientific advice.

2. General principles

2.1 Legislative requirements

Please refer to UK legislation, specifically to the Human Medicines Regulations 2012 (HMRs), as amended. Note that the HMRs have been amended by the Human

Medicines (Amendment etc.) (EU Exit) Regulations 2019 (S.I. 2019/775) and the Human Medicines (Amendment etc.) (EU Exit) Regulations 2020 (S.I. 2020/1488).

Applications for biosimilar products should conform to Regulation 53 (Northern Ireland only), 53A (Great Britain only) or 53B (UK-wide) of the HMRs, depending on the type of application being made.

For products covered by the [compulsory scope of the centralised procedure](https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines#scope-of-the-centralised-procedure-section) (<https://www.ema.europa.eu/en/about-us/what-we-do/authorisation-medicines#scope-of-the-centralised-procedure-section>) (Regulation 726/2004), these must be submitted via the European Medicines Agency (EMA) centralised authorisation procedure in order to be marketed in the European Union (EU) and Northern Ireland. This includes medicines derived from biotechnology processes, which applies to the majority of biosimilar products. In those cases, a licence can only be issued by the MHRA in Great Britain.

For UK-wide or Northern Ireland applications (for products not covered by the compulsory scope), advice should be sought from MHRA.

For risk management, refer to HMRs Schedule 8 paragraphs 12 and 13; Regulations 59(2) to (6); Regulation 61(1) to (14); Regulations 182(2) and 203(2)(d); Schedule 12A paragraphs 22, 23, 24 and 25.

No paediatric investigation plan is required in a biosimilar application.

The Reference Medicinal Product, or Reference Product (RP) is defined in Regulation 48 of the HMRs.

For a Great Britain-only application, RP means a product:

- authorised under Regulation 49(1)(a) of the HMRs, in accordance with the provisions of Regulation 50 of the HMRs; or
- where an EU Marketing Authorisation (MA) was in force on Implementation Period (IP) completion day for EU Exit on 31 December 2020 (IP completion day), but no UK MA is in force because the EU MA was not converted; or
- where a EU MA had ceased to be in force on or before IP completion day but not for reasons to do with efficacy, safety or quality.

Data and Market Exclusivity (DME) for Great Britain-only applications are aligned with Directive 2001/83, with 8 years data exclusivity and a further 2 years market exclusivity.

2.2 Choice of Reference Medicinal Product

The RP must be (or have been) licensed as mentioned in Section 2.1. The Great Britain RP (or RP representative of the Great Britain product) must be used for the comprehensive physicochemical and biological comparability studies, including in vitro analysis. This could include RP sourced from the EU with evidence that the RP is

licensed in the EU via the centralised, decentralised or mutual recognition procedures, providing confirmation that these are the same as the Great Britain RP.

In order to use non-Great Britain RP in clinical studies, evidence should be provided that the non-Great Britain RP is representative of the Great Britain RP, with suitable information (e.g. licensed in EU/European Economic countries (EEA) as described above in section 2.1) or analytical bridging data (refer to CHMP guidance).

In case of doubt, scientific advice is recommended to confirm choice of a suitable RP. Note that all non-Great Britain RP must be authorised in and sourced from a country with similar scientific and regulatory standards (examples would be: EU/EEA, Switzerland, USA, Canada, Australia, Japan).

The RP must have been authorised on the basis of a complete dossier, inclusive of pharmaceutical/quality data, non-clinical testing and clinical trials (i.e., Common Technical Document (CTD) Modules 3, 4 and 5, in addition to Modules 1 and 2).

2.3 Biosimilarity principles

A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorised original biological medicinal product (the RP). The guiding principle of a biosimilar development programme is to establish similarity between the biosimilar and the RP based on a comprehensive comparability exercise, ensuring that the previously proven safety and efficacy of the RP also apply to the biosimilar.

A stepwise approach is recommended throughout the development programme, starting with a comprehensive physicochemical and biological characterisation, followed by a pivotal comparative pharmacokinetic (PK) study.

A biosimilar should be highly similar to the RP in physicochemical properties, biological activity/potency and clinical profiles. In addition, biosimilar development requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concerns. Any observed differences must be duly justified with regard to their potential impact on safety and efficacy. For an active substance that is a protein, the amino acid sequence is expected to be the same, other than justified post-translational modifications.

The posology (dose and frequency of dosing) and route of administration of the biosimilar must be the same as those of the RP but deviations from the RP are possible, such as the strength (for example, higher concentration to allow for a smaller injection volume, more suitable for paediatric indications), pharmaceutical form, formulation, excipients or presentation. These require justification and may need additional data. Patient acceptability should also be considered.

In line with CHMP guidance, there is no regulatory requirement to repeat the demonstration of biosimilarity against the RP (e.g. in the context of a change in the

manufacturing process), once a product licence for the biosimilar has been granted.

In order to support pharmacovigilance monitoring, all appropriate measures should be taken to clearly identify any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to its brand name and batch number.

3. Content of a biosimilar application

3.1 Quality

The CHMP [guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: quality issues](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf) (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf)[lays down the quality requirements for a biological medicinal product claiming to be similar to a RP already granted an MA on the basis of a complete dossier. This CHMP guideline also details the requirements for the manufacturing processes of a biosimilar product and analytical considerations for the expected comparability exercise, including physicochemical properties, purity/impurities, quantity, biological activity and immunochemical properties \(where relevant\). These remain valid and will not be repeated in this MHRA guideline.](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-0.pdf)

The [guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf) (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf) [addresses the extent of the non-clinical studies required to confirm biosimilarity. Differences observed in the physicochemical and biological analyses will require additional in vitro studies, taking into consideration the mechanism of action of the active substance in all the authorised indications of the RP and pathogenesis of the diseases included in the therapeutic indications.](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins-active_en-2.pdf)

The in vitro studies are more appropriately addressed alongside the related quality data in the biosimilar comparability evaluation (CTD Module 3.2.R) and it is recommended that there should not be separate in vitro data reported in the non-clinical (CTD Module 4) section.

Reference medicinal product

The RP used in the biosimilar comparability exercise at the quality level must be clearly identified. For example, it should include the brand name, batch/lot number, source (country where purchased), pharmaceutical form, formulation, strength, number and age of batches at the time of analysis. Where several strengths or presentations are available, their selection should be appropriately justified.

Multiple different batches/lots of RP should be sourced from the appropriate market over a period of time (months to years) to reflect the manufacturing variability of the RP. The RP batches should be stored under the recommended (label) conditions and tested within their approved shelf life. Occasionally, testing of batches past their approved shelf life and stored under long term conditions (for example, frozen at -80°C) may be possible if robust data is provided demonstrating that such storage does not impact the respective quality attributes.

The age of the RP batches (relative to expiry dates) at the time of testing should be considered during the analysis. All RP analytical data generated should be presented in the dossier, in summary tables and annexes. Batch data generated outside the recommended storage conditions and shelf life should be indicated in the summary tables.

The mechanism(s) of action (MOA) should be known and demonstrable, if possible. MOA refers to the initial biological events triggered by the primary binding events of the active substance to known targets (e.g., receptors or antigens), which are potentially relevant to clinical effects; it does not refer to the complete mechanistic understanding of the functional cascade that leads to clinical effects. Critical quality attributes (CQA) should be defined at an analytical and *in vitro* functional level. Functional assays studied should be those relevant to the potential MOA in all therapeutic indications (for example, antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), antibody-dependent cellular phagocytosis (ADCP), apoptosis etc.). A biological event should be considered potentially relevant to the MOA until there is sufficient evidence that it is not relevant; for example, functional assays (ADCC, ADCP and CDC) are not required in case of an RP that primarily targets a soluble antigen.

Multiple different batches of the RP should be used in order to generate a representative quality target product profile (QTPP) and provide robust comparability data. The number of RP batches regarded as sufficient depends on the quality attribute tested and the data generated (e.g., fewer batches of RP would be required for confirmation of higher order structure). For CQA, multiple (tens of) batches sourced over a suitable period of time would be required to provide robust comparability data. Exceptions can be justified in certain cases (for example, for orphan drug products, in the case that less batches of RP are available).

Analytical methods need to be sensitive, qualified and sufficiently discriminatory to detect possible differences. Robust data require the application of suitable orthogonal methods.

Biosimilar comparability exercise

An extensive comparability exercise is required to demonstrate that the biosimilar has a highly similar quality profile when compared to the RP. This should include comprehensive analyses of the proposed biosimilar and RP, using state-of-the-art

methods with suitable sensitivity and orthogonal methods to determine not only similarities but also potential differences in quality attributes. These analyses should include side-by-side comparative studies unless otherwise justified.

Quantitative ranges should be established for the biosimilar comparability exercise, where possible. These ranges should be based primarily on the quality attribute ranges measured for the RP and should not be wider than the range of variability of the RP batches (the QTPP), unless otherwise justified. The relevance of the ranges should be discussed, taking into account the number of RP batches tested, the quality attribute investigated, the age of the batches at the time of testing and the test method used. A descriptive statistical approach to establish ranges for quality attributes can be used, if appropriately justified. However, wide similarity ranges based on inappropriate statistical methods should not be used.

Ideally, batches of the biosimilar candidate would undergo analysis of biological activity (for example, cell-based assays) and in vitro functional activity at the same time as RP batches. Otherwise, an established and characterised in-house reference standard, calibrated against an international reference standard wherever possible, should be employed to minimise day-to-day assay variability.

All relevant batches of the biosimilar candidate, including clinical study batches, stability batches and process performance qualification batches (manufactured at the proposed commercial scale and site) should be analysed and compared with the RP.

Any differences detected in the quality attributes have to be appropriately justified with regard to their potential impact on safety (including immunogenicity) and efficacy. It is not expected that all quality attributes of the biosimilar product are identical to the RP. However, where qualitative and/or quantitative differences are detected, these need to be justified as unlikely to impact on clinical efficacy and safety. Relevant functional and biological head-to-head tests, along with available literature, should be used to provide evidence to support the lack of clinical significance of any difference noted in quality attributes, particularly CQA.

It is recommended that any differences which may have an impact on clinical safety and/or efficacy (for example, increased levels of aggregation or impurities) and cannot be adequately addressed by reference to prior knowledge or by additional characterisation studies, should be reduced by modifications in the manufacturing process. A comparative clinical trial showing equivalent efficacy/safety profile would not be considered an appropriate justification.

The potential impact of a different formulation/excipient(s), container closure system or device should be discussed in terms of product stability and compatibility, as well as acceptability for the patient (for example, citrates may result in injection pain). Justification for why a particular excipient or formulation change is not expected to influence safety or efficacy should be provided.

Release/stability specification limits

It should be noted that similarity ranges used for the biosimilar comparability exercise should be handled separately from release and stability specifications of the biosimilar product (CTD Module 3.2.P.5.1). Release and stability specification limits should be based on knowledge of the CQA of the drug product, biosimilar batch data and data generated from the RP during the biosimilar comparability studies, with limits set to prevent future drift/shift in CQA after demonstration of biosimilar comparability at the time of granting a Great Britain product license.

The specification limits should be suitably justified at the time of approval of the biosimilar, since afterwards each product will have their own lifecycle.

3.2 Non-clinical

In vitro studies should be performed in line with CHMP guidance. It is recommended that all in vitro pharmacology studies are presented in Module 3; this includes studies that are comparative in nature between the biosimilar and the RP and those conducted only with the biosimilar. This is to ensure a clear link between the structural and functional aspects of the biosimilar, allowing evaluation of any differences between the biosimilar and RP, to enable the potential impact of these differences to be assessed. As the same data should not be presented in both Modules 3 and 4, it is acceptable for Module 4 to contain no experimental results, with reference to in vitro data in Module 3.

No in vivo studies from animals are requested as these are not relevant for showing comparability between a biosimilar candidate and its RP: this includes pharmacodynamic studies, kinetic studies and toxicity studies. However, where toxicity studies have been done in compliance with Good Laboratory Practice (GLP), study reports are to be submitted. It is not expected that any review of these would elicit questions from the MHRA, as it is a given that such studies do not contribute to an understanding of comparability. Where such studies have been done with RP that is not the same as that in Great Britain, this should be stated in the non-clinical overview in Module 2.

The non-clinical overview, in Module 2, should be brief but it should explain why any in vivo studies were done (for example, at the request of another regulatory body) and it should give a discussion of the reasons for use of any excipient used in the biosimilar product that is not in the RP.

Where investigations in the quality dataset suggest the possibility that a biosimilar candidate may not be highly similar to the RP, conduct of in vivo studies in animals does not contribute to resolving this and in vivo studies should not be done with this intent. If there are a number of differences, or differences which cannot be ruled out as having no clinical impact, development as a new biological product should be considered. Safety studies should not be done to characterise a newly identified impurity in either the RP or the biosimilar candidate.

Excipients

Use of excipient(s) in the proposed biosimilar product that are not used in the RP is not encouraged from a biosimilarity perspective. However, changes which may benefit patients (for example, to reduce injection pain or stinging) are encouraged and should be carefully considered. Where different excipient(s) are used, there could be instances where this would be the first time that the excipient had been used by this route; a discussion should be presented that addresses the safety of that excipient by the route intended.

It is anticipated that in most instances, there will be use of the excipient(s) by the route intended at similar amounts with other products and if so, a discussion to establish this can be sufficient. However, if a novel excipient, or a novel route for an excipient, is used in the proposed biosimilar product, this should be justified, and includes the possibility that results from new safety studies are presented, if appropriate. As studies intended to characterise the safety of the excipient, compliance with GLP is expected.

Applicants are encouraged to seek scientific advice if they intend to make changes to the excipients.

Relation to other guidelines

The MHRA is aware that a range of guidelines may exist that require in vivo studies to support development of biosimilar products. The MHRA is aware that companies will not develop products only for the Great Britain market and that developers need to meet requirements of other regulators. Nevertheless, the content of Module 4 for the Great Britain can be limited to those studies that are GLP compliant, requirements of other regulators notwithstanding. In this case, Module 4 in the Great Britain may not be part of the CTD supporting the product in other regions and the MHRA will accept this deviation.

3.3 Clinical

Confirmatory pharmacokinetic (PK) trial

The clinical comparability exercise should always include a pivotal comparative PK trial, which may include the measurement of pharmacodynamic (PD) markers if available. It is strongly recommended to use biosimilar product derived from the commercial manufacturing process representing the quality profile of the batches to be commercialised.

The PK trial should be designed and powered to demonstrate equivalence to the RP, preferably in healthy volunteers. The design should be robust and justified, including the choice of crossover or parallel design. A crossover design is more sensitive to detect differences but may not be suitable for RP with a long half-life or notable

immune response. If appropriate population PK or PK-PD models are available for the RP in the literature, modelling and simulation should be considered for optimising study design – for example, selection of the most sensitive dose(s) and study population to detect PK differences, and choice of sample size.

Linear (nonspecific) clearance and nonlinear (target-mediated) clearance should be addressed – for example, through dose selection and assessment of partial areas under the curve (AUCs). Protein content adjustments or covariates to be used in the statistical analysis of a parallel group trial (e.g., body weight, subject sex) should be predefined in the statistical analysis plan. The equivalence margins must be prespecified; an interval of 80.00 - 125.00% is generally acceptable.

The PK trial should demonstrate equivalence of the primary PK parameters, usually $AUC_{0-\infty}$ and Cmax. If the extrapolated portion of $AUC_{0-\infty}$ makes up >20% of the total $AUC_{0-\infty}$ in >20% of observations this requires discussion of the validity of the study. In the event of a failed PK study (i.e., 90% confidence intervals for the primary PK parameters are not contained completely within the pre-specified acceptance limits), root cause analysis should be provided with conclusions adequately reflected in the planning and conduct of a subsequent PK study. If no root cause is identified and another study is conducted and is positive, the initial study should not be ignored when reaching conclusions on PK similarity.

If available, PD parameters can be measured during the PK trial and descriptive results should be presented to support a conclusion of biosimilarity.

In all cases, safety and immunogenicity data should be collected during this trial and should be presented. These specifically include injection site or infusion-related reactions, anti-drug antibody (ADA) rate and kinetics as well as assessment of their impact on PK (and PD) through prespecified group analysis of ADA-negative and ADA-positive subjects. In vitro immunogenicity tests may help support the functional comparability exercise but would not substitute for the immunogenicity assessment in the PK trial.

Confirmatory efficacy trial

Although each biosimilar development needs to be evaluated on a case by case basis, it is considered that, in most cases, a comparative efficacy trial may not be necessary if sound scientific rationale supports this approach. Therefore, a well-argued justification for the absence of an efficacy trial should be appended to CTD Module 1 of the submitted application.

Applicants are encouraged to seek scientific advice to discuss this approach as soon as they have sufficient comparative analytical and functional data to support it. However final acceptance of this approach would only be considered after submission of the complete data package. The general principles to be used in this justification are summarised hereafter.

Justification for comparable efficacy

Although precise correlations between clinical efficacy and pharmacological effects are usually lacking, the efficacy of the RP can usually be related to the biological events triggered by the binding of the active to its known targets. Therefore, a justification should be provided that comparable efficacy can be derived from comparable binding properties and functional characteristics. Any observed differences must be justified as not clinically relevant, based on specific experiments and available literature.

Justification for comparable safety and immunogenicity

The safety profile of the RP is largely predicted from on-target side effects, i.e., exaggerated and adverse pharmacologic effects at the target, including on normal tissues. Other common adverse drug reactions (ADR) are injection-related reactions, which are triggered by various mechanisms, some being mediated by ADAs. Extensive clinical experience with the RP informs a risk-based assessment of the immunogenicity of the biosimilar, potential rates of binding or neutralising ADAs and their clinical relevance. Justification for comparability of the biosimilar is informed by clinical experience and quality attributes of the RP, not whether the immunogenicity and safety risks are low or high.

The quality attributes, including drug product characteristics (protein aggregates, impurities) and formulation of the biosimilar candidate should form the basis for justification that safety and immunogenicity are comparable to those of the RP.

This argument should be supported by data from the confirmatory PK trial showing comparable safety and immunogenicity to the RP.

Need for an efficacy or safety trial

There may still be cases requiring a comparative efficacy/safety trial, mainly where there is a lack of understanding of the biological functions of the RP related to its clinical effects or where the relevant CQA may not be sufficiently characterised due to analytical limitations.

Exceptionally, additional clinical safety data may be required where safety uncertainties cannot be resolved without patient exposure pre-licensing. For example, where serious ADRs to the RP have unpredictable root causes (e.g., pure red cell aplasia with epoetin), exposure of a significant patient cohort to the biosimilar candidate is considered the most appropriate approach to resolve any residual uncertainty around safety and immunogenicity.

Applicants are encouraged to seek scientific advice to discuss the design of any potential additional study. The results of an efficacy/safety trial conducted upon request of other Regulatory Agencies should be submitted within the MA application.

Indications claimed for the biosimilar candidate

Once a biosimilar candidate has been shown to be highly similar to the RP in terms of analytical characteristics and functional properties related to the MOA of the RP (see section 3.1), all the indications granted to the RP can be claimed by the biosimilar candidate without further justification, provided they are not protected by market exclusivity or patent.

3.4 Product labelling

The content of the summary of product characteristics (SmPC) for a biosimilar should be consistent with that of the RP (i.e., the information from the RP SmPC that applies to the biosimilar should be included in its SmPC).

The indications in section 4.1 should be in line with the indication of the RP. If the biosimilar does not have strength(s) and/or pharmaceutical form(s) that exist for the RP and are used in some subsets of the authorised patient population (for example, paediatric population), this should be mentioned in section 4.2 of the SmPC. An example of such wording is: “[Invented Name] is only available as [description of the pharmaceutical form]. Thus, it is not possible to administer [Invented Name] to paediatric patients that require less than a full [x] dose. If an alternate dose is required, other medicinal [INN] products offering such an option should be used.”

Section 5.1 should include the following statement: “[Invented Name] is a biosimilar medicinal product. Detailed information is available on the MHRA website”.

The Applicant should discuss and justify any differences of the proposed SmPC to that of the RP, for example, in relation to a different device. Consideration should be given to components of any devices, particularly those which may result in adverse events (for example, latex).

In line with the CHMP approach, it may also be possible to justify a simplification of the immunogenicity data provided in the RP’s SmPC, i.e., omitting specific ADA rates as these are dependent on the assays used, which have greatly improved over time, and are not necessarily relevant.

The package leaflet should reflect the scientific content of the SmPC of the biosimilar, for the relevant information for patients. With the exception of differences based on scientific grounds, deviations from the RP package leaflet are expected to be justified by results of user testing consultation with target patient groups.

Like any biological medicine, biosimilars are subject to additional monitoring after MA and the product information carries a black inverted triangle (▼).

3.5 Risk management plan (RMP)

The RMP for a biosimilar candidate should reflect that of the RP in terms of safety concerns, additional pharmacovigilance activities and additional risk minimisation. If

there are additional safety concerns for the biosimilar candidate these are unlikely to be due to the active molecule but rather factors such as excipient or device that are different from the RP. These should be included in the RMP.

Where ongoing additional pharmacovigilance activities are required for the RP (for example, participation in ongoing disease registries), these should also apply to the biosimilar candidate. Where possible, this would be through collaboration or participation in those studies or registries already in place for the RP, or otherwise in other existing disease studies or registries. This will enable collection of real-world information to support characterisation of risks and signal detection of potential safety signals related to the RP and its biosimilars.

Any additional risk minimisation measures that continue to be required for the RP should also be implemented for the biosimilar candidate, for example educational materials for healthcare professionals and patients or patient alert cards.

4. Traceability

In the post-authorisation phase as a result of manufacturing, product variability over time within and across products with similar active substances is possible. Therefore, a key requirement for pharmacovigilance of biosimilars is the need 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.

Biosimilars have the same International Nonproprietary Name (INN) as the RP and must be readily distinguishable, preferably with an invented brand name. Of note, the INN followed by the name of the MA holder is not recommended, whereas this is allowed by the EMA. The use of an invented brand name will allow newly emerged and potential product-specific safety concerns to be rapidly identified and evaluated throughout the product lifecycle, and for the product to be traceable to location and patients.

Accurate traceability of biosimilars by brand name and batch number must be assured in the post-marketing setting. The importance and method of traceability needs to be highlighted in the product information and on the product packaging or labelling as appropriate. For example, removable sticky labels on the product detailing brand name and batch number that can be recorded on patient records or 3D barcoding may be more appropriate for electronic records.

Traceability should be fully integrated in the healthcare settings, for example, electronic data recording and record linkage etc. Where necessary, additional training to healthcare professionals should be provided to support reporting of brand name and batch number when reporting adverse reactions.

5. Interchangeability

Once authorised, a biosimilar product is considered to be interchangeable with their RP, which means a prescriber can choose the biosimilar medicine over the RP (or vice versa) and expect to achieve the same therapeutic effect. Likewise, a biosimilar product is considered to be interchangeable with another biosimilar to the same RP.

As a result of interchangeability, switching patients from one product to another (RP or biosimilar) has become clinical practice. The decision rests with the prescriber in consultation with the patient, in line with the principles of shared decision making; both need to be aware of the brand name of the product received.

All biological medicines, including biosimilars, should be prescribed by brand name.

6. Substitution

Substitution at the pharmacy level without consulting the prescriber is not permitted for biological medicines, including biosimilars.

7. Further information

Broader guidance to stakeholders and links to educational resources are given in the NHS England publication '[What is a biosimilar medicine?](#)'

(<https://www.england.nhs.uk/publication/what-is-a-biosimilar-medicine/>)

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