Guidelines for Registration of Biosimilar Products in Bangladesh 2025

Directorate General of Drug Administration
Ministry of Health and Family Welfare
Government of the People's Republic of Bangladesh

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AUTHORIZATION LETTER

Subject: Official Authorization and Endorsement of the "Guideline for Registration of Biosimilar Products in Bangladesh 2025"

This letter officially confirms and authorizes that the document titled "Guideline for Registration of Biosimilar Products in Bangladesh 2025" is the officially approved, current, and mandatory regulatory framework for the evaluation and registration of biosimilar products in Bangladesh. This updated Guideline supersedes the previously issued "Guideline for Registration of Biosimilar Products in Bangladesh 2018."

The Director General, Directorate General of Drug Administration (DGDA), confirms that the new guideline was developed through a robust process, ensuring its scientific integrity and international alignment. The Guideline was prepared following a comprehensive scientific review, incorporation of expert opinions, collection of public feedback, and consultation with relevant stakeholders.

Crucially, the revised version has been fully aligned with the World Health Organization (WHO) Technical Report Series No. 1043, Annex 3. This alignment ensures that Bangladesh's regulatory standards for biosimilar product registration meet international benchmarks, thereby upholding public health safety and promoting access to quality biosimilar medicines.

This authorization confirms that the "Guideline for Registration of Biosimilar Products in Bangladesh 2025" is the sole regulatory document for the registration of biosimilar products in the country, which is effective immediately.

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Message from the Director General, Directorate General of Drug Administration

Biosimilar medicines are playing an increasingly critical role in the management of complex, chronic, and life-threatening diseases such as cancer, autoimmune disorders and diabetes. These medicines are often highly costly; therefore, making them affordable is essential to ensure wider access to advanced treatment options for the people of Bangladesh. However, ensuring their quality, safety and efficacy is essential before they are made available to patients.

Recognizing the growing importance of biosimilars, Directorate General of Drug Administration (DGDA) has developed this guideline on evaluation of biosimilars to provide a structured regulatory framework for the assessment and approval of biosimilar products. This guideline reflects international best practices aligned with WHO, ICH and other globally accepted scientific principles, adapted to the national context of Bangladesh.

Biosimilars are not generics. Due to the complex structure and sensitive manufacturing processes of biological medicines, minor differences in production can significantly impact the safety or effectiveness of a biosimilar. Therefore, it is imperative that manufacturers demonstrate similarity to a reference biologic through a stepwise approach involving analytical, non-clinical, and clinical evaluations.

Importantly, this guideline emphasizes the 3Rs principle of animal ethics — Replacement, Reduction, and Refinement — in non-clinical studies. By promoting advanced scientific methods that reduce reliance on animal testing where scientifically justified, we can not only ensure ethical compliance but also minimize the cost of development, ultimately translating into more affordable biosimilar medicines for the people of Bangladesh.

The successful implementation of this guideline will strengthen regulatory oversight, build confidence in biosimilar products and ensure that Bangladeshi patients have access to safe, effective, and high-quality treatment alternatives. It will also encourage local and international manufacturers to invest in the development of biosimilars under a predictable and transparent regulatory pathway.

I extend my sincere thanks to all stakeholders for their contributions to this important initiative. I urge healthcare professionals, the pharmaceutical industry, academic institutions and regulatory staff to work collaboratively to ensure the effective application of this guideline.

Major General Md. Shameem Haidar
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05 NOV 2025

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Contents

Abbreviations

ADA	anti-drug antibody
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
CDC	complement-dependent cytotoxicity
C1q	complement component 1q
Fab	antigen-binding fragment
Fc	fragment crystallizable
FIIa	activated blood coagulation factor II
FXa	activated blood coagulation factor X
G-CSF	granulocyte-colony stimulating factor
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
Ig	immunoglobulin
INN	international nonproprietary name
IS	international standard(s)
IU	International Unit(s)
mAb	monoclonal antibody
NRA	national regulatory authority
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
RP	reference product
SD	standard deviation
TNF	tumour necrosis factor

1. Introduction

Biotherapeutic products (biotherapeutics) have a successful record in treating many life-threatening and chronic diseases. The expiry of patents and/or data protection periods for a number of such biotherapeutics has ushered in an era of products that are designed to be highly "similar" to the corresponding registered "originator" product. Based on a comprehensive head-to-head comparison and demonstrated high similarity, such products can partly rely for their registration on safety and efficacy data obtained for the originator products. A variety of terms have been used to describe these products, including "biosimilars", "similar biotherapeutic products", "similar biological medicinal products" and "biosimilar products". For the sake of clarity, the term "Biosimilar" will be used for registration process in DGDA.

This guideline is intended to assure the quality, safety and efficacy of Biosimilar products manufactured or imported for purposes of the submission of registration/marketing authorization application under The Drugs and Cosmetics Act, 2023. For public health purposes, it is essential that the standard of evidence supporting the decision to register a biosimilar is sufficiently high to ensure that the product meets acceptable levels of quality, safety and efficacy. Elaboration of the data requirements and considerations for the licensing of such products is expected to facilitate the development of and worldwide access to biological products of assured quality, safety and efficacy at more affordable prices.

It is expected that these DGDA Guidelines on the scientific principles for evaluating biosimilars will help to harmonize global standards and lead to easier and speedier approval and assurance of the quality, safety and efficacy of these products. It is important to note that biological products that are not shown to be similar to an RP as set out in these Guidelines should not be described as "similar" and should not be termed "biosimilars".

2. Purpose and scope

This Guideline is intended to provide globally acceptable principles for the registration/Marketing Authorization of biological products that are claimed to be similar to biological products of assured quality, safety and efficacy that have been registered based on a full licensing/CTD dossier. On the basis of proven similarity, the registration of a biosimilar would in part rely on nonclinical and clinical data generated for an already registered originator product. The Guideline applies to biosimilar products that can be well characterized, such as recombinant DNA-derived therapeutic peptides and proteins. Some of the principles provided in these Guidelines may also apply to recombinant analogues of plasma-derived products. Vaccines and plasma-derived products are excluded from the scope of these Guidelines.

3. Terminology

3.1. Biosimilar: a biological product that is shown to be highly similar in terms of its quality, safety and efficacy to an already licensed reference product.

3.2. Comparability/similarity exercise: direct head-to-head comparison of a biological product with a licensed **reference product** with the goal of establishing similarity in quality, safety and efficacy.

3.3. Comparability margin: the largest difference that can be judged as being clinically acceptable.

3.4. Comparability/similarity range: predefined allowable differences in physicochemical properties and biological activity level.

3.5. Drug product: a pharmaceutical product that typically consists of a drug substance formulated with excipients.

3.6 Drug substance: the active pharmaceutical ingredient and associated molecules that are typically formulated with excipients to produce the **drug product**. This may also be referred to as the "active substance" in other documents.

3.6 Efficacy study: a clinical trial to compare the efficacy of the biosimilar to the reference product.

3.7. Excipient: a constituent of a medicine other than the drug substance, added in the formulation for a specific purpose. While most excipients are considered inactive, some can have a known action or effect in certain circumstances (for example, hyaluronidase). The excipients may differ for a biosimilar and its reference product and need to be declared in the labelling and package leaflet of the medicine to ensure its safe use.

3.8. Equivalent: equal or highly similar in the parameter of interest. Equivalent quality, safety and efficacy of two medicinal products denotes that they can be expected to have similar (no better and no worse) quality, safety and efficacy, and that any observed differences are of no clinical relevance.

3.9. Generic medicine: a medicine that is structurally identical to an originator product (comparator) for which the patent and/or data protection period has expired.

3.10. Head-to-head comparison: direct comparison of the properties of a biosimilar with its corresponding reference product. Comparison based on historical data is not acceptable.

3.11. Immunogenicity: the ability of a substance to trigger an immune response or reaction (for example, development of specific antibodies, T-cell response, or allergic or anaphylactic reaction).

3.12. Impurity: any component present in the drug substance or drug product that is not the desired product, a product-related substance or excipient (including buffer components). Impurities may be either process or product related.

3.13. Marketing authorization holder: any person or legal entity that has received a marketing authorization or licence to manufacture and/or distribute a medicine. It also refers to a person or legal entity allowed to apply for a change to the marketing authorization or licence. Under the same licence, the marketing authorization holder could have several manufacturing sites registered. Therefore, several manufacturers could be involved.

3.14. Non-inferior: not clinically inferior to a comparator in the parameter studied. A non-inferiority clinical trial is one that has the primary objective of showing that the response to the investigational product is not clinically inferior to that of a comparator within a pre-specified margin.

3.15. Originator product: a medicine that has been licensed by an NRA on the basis of a full registration dossier – that is, the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.

3.16. Pharmacodynamic study: a clinical study that measures a pharmacodynamic (PD) response that effectively demonstrates the characteristics of the product's target effects. PD biomarkers for biosimilars do not need to be surrogate end-points for clinical efficacy outcomes.

3.17. Pharmacovigilance: the science and activities relating to the detection, assessment, understanding and prevention of adverse effects caused by medical drugs.

3.18. Posology: dosage for each indication and each method/route of administration. Information includes dose recommendation (for example, in mg, mg/kg or mg/m2), frequency of dosing (for example, once or twice daily, or every 6 hours) and treatment duration.

3.19. Reference product (RP): a biological product used as the comparator in a direct head-to-head comparability exercise with a biosimilar in order to demonstrate similarity in terms of quality, safety and efficacy. Only an originator product licensed on the basis of a full registration dossier and marketed for a suitable period of time with proven quality, safety and efficacy can serve as an RP.

3.20. Reference standard: a measurement standard such as an international, pharmacopoeial or national standard – it should be noted that reference standards are distinct from reference products and serve a different function.

3.21. Similarity: absence of any relevant difference in the parameter(s) of interest.

4. Scientific considerations and concept for registration of biosimillars

- Characterization and evaluation of the quality attributes of the RP should be the first step in guiding the development of the biosimilar. This is followed by a comparability exercise applying sensitive orthogonal analytical methods and assays to demonstrate structural, functional and clinical similarity. Comprehensive characterization and comparison showing similarity at the quality and nonclinical (in vitro) level are the basis for establishing comparability, with a tailored confirmatory clinical data package required for registration.
- If differences between the biosimilar and the RP are found, the underlying reasons for them should be investigated. Unless such differences are explained and justified in terms of lack of clinical impact, additional data (for example, on safety) may be required.
- The standalone development of biological products is not discussed in the current Guidelines. In addition to quality and nonclinical (in vitro) data, clinical data are generally required for any biosimilar. The type and amount of such data considered to be necessary will depend on the product or class of products, on the extent of characterization possible using state-of-the-art analytical methods, on observed or potential differences between the biosimilar and the RP and on clinical experience with the RP (for example, safety/immunogenicity concerns in a specific indication). A case-by-case approach will be needed for each class of products.
- A biosimilar is intended to be highly similar to a registered biological product for which substantial evidence exists of its safety and efficacy. Manufacturers should demonstrate both a full understanding of their product and consistent and robust manufacture and should submit a full quality dossier that includes a complete characterization of the product.
- Comparison of the biosimilar and the RP with respect to quality represents an additional element to the "traditional" full quality dossier. Such comparison will include a comprehensive comparison of biological function at the in vitro level.
- A reduction in data requirements is therefore possible for the nonclinical in vivo and/or clinical parts of the development programme.
- The posology and route of administration of the biosimilar should be the same as for the RP. Studies must be comparative in nature and must employ state-of-art analytical methods capable of detecting potential differences between the biosimilar and the RP.
- The main clinical studies should use the final formulation of the biosimilar (that is, derived from the final process material); if not, then additional evidence will be required to demonstrate that the biosimilar to be marketed is comparable to that used in the main clinical studies. If similarity between the biosimilar and the RP has been demonstrated, the biosimilar may be approved for all clinical indications of the RP supported by appropriate scientific data and justification.

5. Key principle for registration of biosimilars

- Characterization of the quality attributes of the RP should be the first step in guiding the development of the biosimilar. The subsequent comparability exercise should demonstrate structural, functional and clinical similarity.
- Demonstration of similarity of a biosimilar to an RP in terms of structural and functional aspects is a prerequisite for establishing comparability, with a tailored clinical data package required as needed.
- A clinical bioequivalence trial with pharmacokinetic (PK) and pharmacodynamic (PD) parameters (if available), and including an assessment of immunogenicity in human subjects, will typically be a core part of the clinical comparability assessment, unless scientifically justified.
- The decision to register a biosimilar should be based on evaluation of the whole data package generated during the overall comparability exercise.
- If relevant differences between the proposed biosimilar and the RP are found at the structural, functional or clinical level, the product is unlikely to qualify as a biosimilar.
- If comparability exercises are not performed as outlined in this document then the final product should not be referred to as a biosimilar.
- Biosimilars are not "generic medicines" and the authorization process for such medicines generally does not apply.
- As with other biological products, biosimilars require effective regulatory oversight pre- and post-approval in order to manage the potential risks they pose and to maximize their benefits.

6. Reference product

Comprehensive information on the reference product (RP) provides the basis for establishing the quality, safety and efficacy profile against which the biosimilar will be compared. The RP also provides the basis for dose selection and route of administration, and is used in the similarity studies required to support the registration application. Demonstration of a high level of analytical and functional similarity between the biosimilar and RP provides the rationale for a tailored nonclinical and clinical dataset to support the application for marketing authorization of the biosimilar. The information needed to support the acceptability of an RP sourced from another jurisdiction will be determined by the DGDA.

The posology/Indication and route of administration of the biosimilar should be the same as that of the RP. However, depending on the jurisdiction, the strength, pharmaceutical form, formulation, excipients and presentation (for example, use of a different medical device or number of syringes in a pack) of the biosimilar might differ from the RP, if justified. The acceptability of additional routes of administration following approval of the biosimilar will also depend upon the jurisdiction. Since the choice of RP is crucial in the development of a biosimilar, the following should be considered:

- The RP should have been licensed/registered on the basis of a full standalone set of quality, nonclinical, safety and efficacy data. A biosimilar should therefore not be accepted as an RP.
- There should be sufficient information available to support the safe and efficacious use of the RP.
- For the registration of a specific biosimilar, a single biological product from one marketing authorization holder should be chosen and defined as the RP (By DGDA). The entire comparability exercise should be performed against that RP. However, as outlined

below, it may be possible to use the same RP sourced from another jurisdiction in clinical studies.

- RP marketed in another jurisdiction (non-local) is allowed by DGDA-the RP should be licensed/registered in a jurisdiction that has an established regulatory framework, as well as experience with the evaluation of biological products and post-marketing surveilance activities. It is important to note that the acceptance of a non-local RP for the evaluation of a biosimilar in Bangladesh does not imply that DGDA has approved the RP for use in the domestic market.
- If the RP is not available anymore or there is confusion regarding which one should be selected for RP (like in Human Insulin), DGDA will give final decision regarding selection of RP.

7. Quality evaluation

The comparison showing molecular similarity between the biosimilar and the RP provides the essential rationale for predicting that the clinical safety and efficacy profiles of the RP apply to the biosimilar. Therefore, a high degree of analytical and functional similarity between the biosimilar and the RP is the basis for developing a biosimilar.

Development of a biosimilar involves the thorough characterization of multiple RP batches ((at least three batches of RP)) in order to obtain an understanding of the overall quality profile as well as the range of variability of the RP batches on the market. Based on the knowledge gained from the RP characterization studies, as well as available in-house and public information, the manufacturing process of the biosimilar is developed to produce a product that is highly similar to the RP in all clinically relevant quality attributes (that is, attributes that may impact clinical performance).

The biosimilar documentation should comply with the originator products or standard set by DGDA. Full quality dossiers for both drug substance and drug products are always required for each class of products according to the relevant guidelines. The manufacturer of the biosimilar should additionally carry out a comprehensive and comparative state-of-the-art physicochemical and biological characterization of the biosimilar and the RP and document the results in the submitted dossier.

7.1. International reference standards

According to WHO there are international standards (IS) and reference reagents, which serve as reference sources of defined biological activity expressed in International Units (IU) or Units (U).These materials are intended for use in the calibration of bioassays and are available for a wide range of substances including hormones (for example, erythropoietin, follicle-stimulating hormone) and cytokines – for example, granulocyte-colony stimulating factor (G CSF) – as well as modified/long-acting proteins (such as pegylated G-CSF, darbepoetin and etanercept) and monoclonal antibodies (mAbs). IS for the latter product class are expanding and currently include standards for adalimumab, bevacizumab, infliximab, rituximab and trastuzumab. These standards are produced according to defined criteria as per WHO recommendations and often contain excipients which optimize the retention of biological activity and other important characteristics as well as ensuring stability, but which may also interfere with physicochemical methods. The standards are important for assay development, for qualifying and validating assays for their intended use, for monitoring the potency of individual/diverse products, for calibrating bioassays (either directly or to calibrate national or pharmacopoeial standards) and for supporting assay performance throughout the life-cycle of a product.

For biological medicines, expression of potency in units of bioactivity relative to an independent standard is an essential regulatory tool for harmonizing product dosing for patients globally. It

should be noted however that with the development of innovative products the role of the IS in potency determination is changing and decisions on potency and labelling are likely to be made on a case-by-case basis depending on the product and the situation that exists when the biosimilar is developed. For example, for naturally derived proteins such as coagulation factors and hormones (for example, erythropoietin and follicle-stimulating hormone), where the establishment of the IS with an assigned IU preceded the development of versions derived from recombinant DNA (rDNA), the practice of using the IU for potency assignment, dosage and product labelling is well established, and where applicable this has continued for biosimilars.

However, the situation is different for non-natural and engineered proteins such as mAbs. Since IS did not exist when the innovator products were developed, such products were licensed and marketed for clinical use with potency described by manufacturers in proprietary units relative to their in-house product-specific reference material, with product dosing and labelling given in mass units.

The practice of determining potency relative to an in-house qualified reference material and of using mass units for dosing/labelling has also been implemented by biosimilar manufacturers and is expected to continue. In this situation, manufacturers should develop a well characterized product-specific in-house reference material calibrated against the IS (where this exists) with a regulatory expectation that the implementation and management of this in-house reference material (two-tiered approach) will be conducted as per regulatory guidance.

Consistent with the biosimilarity paradigm, the retrospective establishment of an IU value should not affect the potency of the biosimilar (which should be aligned with the RP) and should not affect the labelling or dosing regimens of existing or future products.

It is important to note that WHO IS and other WHO reference standards are not medicinal products (even though the drug substance in then may be derived from material that was produced at clinical grade) and are distinct (for example, in terms of protein content, formulation etc.) from the RP which has an established clinical history and is an essential component of the biosimilarity route to licensure.

The RP defines the quality target product profile (QTPP) that a biosimilar must meet as per the principles of biosimilarity – a function that the reference standard does not serve. Instead, the IS defines the IU of bioactivity for the calibration of bioassays (either directly or through the calibration of manufacturer reference materials) and thus plays an essential role in the development of suitable assay methods. It should further be noted that the IS cannot be used to determine a product's specific activity, dictate the quality of acceptable biosimilars for regulatory purposes or demonstrate biosimilarity, and should therefore not be misused as a comparator for biosimilar development (3–5). Importantly, the IS:

(a) allows for an understanding of consistency in bioactivity across batches of a product throughout its life-cycle;

(b) provides continuity with respect to the in-house reference material and supports transition (change) as the product evolves;

(c) facilitates the harmonization of bioactivity across different products (both RPs and biosimilars); and

(d) increases confidence in the quality of globally available biosimilars.

7.2. Manufacturing process

The manufacturing process of the biosimilar should be developed based on a comprehensive understanding of the RP gained through detailed characterization studies of a sufficient number of RP batches.

In order to produce a high-quality product as similar as possible to the RP, the biosimilar manufacturer should assemble all available knowledge on the RP regarding the type of host cell, product formulation and the container closure system used for marketing. Although the biosimilar does not need to be expressed in the same type of host cell as that used for the RP, it is recommended that a similar host cell type is used (for example, Escherichia coli, Chinese hamster ovary cells, etc.). This will reduce the potential for critical changes in the quality attributes of the protein, or in post-translational modifications, product-related impurities or the process-related impurity profile, that could potentially affect clinical outcomes and immunogenicity.

If a different host cell is used (for example to avoid unwanted and potentially immunogenic glycan structures present in the RP) then changes introduced in terms of product-related substances, as well as product- and process-related impurities, need to be carefully considered.

The manufacturing process used can significantly affect the structure of the drug substance and thereby impact upon the potency of the product. For example, in the case of mAbs, when deciding upon the expression system to employ, manufacturers should be guided by the potential for both enzymatic and non-enzymatic modifications, such as incomplete disulfide bond formation, formation of aggregates, glycosylation, N-terminal pyroglutamine cyclization, C-terminal lysine processing, deamidation, isomerization and oxidation, modification of the N-terminal amino acids by male uric acid, and amidation of the C-terminal amino acid.

The manufacturer must demonstrate the consistency and robustness of the manufacturing process by implementing state-of-the-art quality control and assurance procedures, in-process controls and process validation.

The biosimilar manufacturing process should meet the same standards required for originator products, including manufacture under current good manufacturing practices (preferably recommended by WHO/other comparable international standard).

As for any biological product, if process changes are introduced during the development of a biosimilar then the impact of the changes should be assessed through a comparability exercise (2, 6). Although many of the same principles are followed, the assessment of manufacturing process changes should be addressed separately from the comparability exercise performed to demonstrate biosimilarity with the RP (see section 7.4 below).

7.3. Analytical considerations

Thorough characterization of both the RP and the biosimilar should be carried out using state-of-the-art chemical, biochemical, biophysical and biological analytical techniques.

The methods should be scientifically sound and demonstrated to be of appropriate sensitivity and specificity for their intended use. Details should be provided on primary and higher-order structure, post translational modifications (including, but not limited to, glycoforms), biological activity, purity, impurities, product-related (active) substances (variants) and immunochemical properties, where relevant.

Orthogonal methods must be used, as far as possible – that is, the variants and quality attributes of the product should be analysed using analytical methods with different underlying chemical, physical and biological properties. For example, ion exchange chromatography, isoelectric focusing and capillary electrophoresis all separate proteins based upon charge but do so under different analytical conditions and on the basis of different physicochemical properties of the biological product. As a result, one method may detect variants that another method does not.

The goal of the comparability investigation is to be as comprehensive as possible in order to minimize the possibility of undetected differences between the RP and the biosimilar that may affect safety and clinical activity. The analytical limitations of each technique (for example,

limit of detection or resolving power) should be considered when determining the similarity of a biosimilar to its RP.

Representative raw data should be provided for analytical methods (for example, high-quality reproductions of gels and chromatograms) in addition to tabular data summarizing the complete dataset and showing the results of all release and characterization analyses carried out on the biosimilar and the RP.

Graphical presentation of data sets comparing biosimilar and RP analytical data should also be produced where possible. The results should be accompanied by sufficient interpretation and discussion of the findings.

The methods used to measure quality attributes for batch release should be validated in accordance with relevant guidelines, as appropriate. A complete description of the analytical techniques employed for release and characterization of the product, along with method validation or qualification data (as appropriate), should be provided in the Marketing Authorization/Registration application.

Due to the unavailability of drug substance for the RP, the biosimilar manufacturer will usually be using a commercial drug product for the similarity exercise. The commercial drug product will, by definition, be in the final dosage form containing the drug substance(s) formulated with excipients. It should be verified that these excipients do not interfere with the analytical methods used and thus have no impact on test results.

If the drug substance in the RP needs to be purified from a formulated reference drug product in order to be suitable for characterization then studies must be carried out to demonstrate that product heterogeneity and relevant attributes of the active moiety are not affected by the isolation process.

The approach used for isolating the drug substance of the RP and comparing it with the biosimilar should be justified and demonstrated (with accompanying data) to be appropriate for the intended purpose.

7.4. Characterization of Biosimilar

Characterization of a biotechnological/biological product by appropriate techniques, as described in ICH Q6b, includes the determination of physicochemical properties, biological activity, immunochemical properties (if any), purity, impurities, contaminants and quality.

- Biosimilarity is evaluated using a scientifically tailored approach, with approval based on the "totality of the evidence," including analytical, (structural and functional), animal toxicity, pharmacokinetic (PK), pharmacodynamic (PD), immunogenicity, and clinical safety and effectiveness.
- Collecting data from publicly available information and data from extensive analytical characterization for different batches of the reference product, will enable the applicant to:

  -Achieve the quality target product profile (QTPP) of the proposed biosimilar.

  -Detect batch to batch variation within batches of the same reference product.

  -Specify the acceptance criteria for biosimilarity with justification.
- For differences in quality attributes with higher criticality, functional assays to thoroughly address their possible clinical impact are generally expected. Where there are confirmed differences in the most critical quality attributes it will be more challenging to justify the conclusion that the product is a true biosimilar.
- Confirmed differences in low criticality quality attributes also need to be adequately considered, but in the case of such differences reference to available information (which could, for example, originate from scientific publications) is usually sufficient.

used in comparative studies) (see ICH Q6B for additional details).

- For product with multiple biological activities, manufactures should perform, as part of the product characterization, a set of relevant function assays designed to evaluate the range activities of the product.

- In case of mAb, further information on Fc-mediated Functions should be provided and compared for example, antibody-dependent cellular cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC), where relevant.

- The results of relevant biological assay(s) should be provided and expressed in units of activity calibrated against an international or national reference standard, where available and appropriate.

- Various methods such as surface plasmon resonance, microcalorimetry, or classical scatchard blot can provide information on the kinetics and thermodynamics of binding. Such information can be related to the functional activity and characterization of the proposed product's higher order structure.

- These assays should comply with appropriate international pharmacopoeia requirements for biological assays, as applicable.

7.7. Purity and impurities

Identification of product and process impurities should be performed using orthogonal testing. - The purity and impurity profiles of the proposed biosimilar product and RP should be compared both qualitatively and quantitatively by a combination of analytical procedures.

- Appropriate state-of-the art methods should be used to compare the product-related substances and impurities. This comparison should take into account specific degradation pathways (for example: oxidation, deamidation, aggregation, truncation, charge variants, visible, sub-visible and sub-sub visible particle, etc.) of the biosimilar product and potential post-translational modifications of the proteins.

- The manufacturer should characterize, identify, and quantify in the proposed biosimilar product and the reference product, to the extent feasible.

- If a comparative physicochemical analysis reveals comparable product-related impurities at similar levels between the two products, pharmacological/toxicological studies to characterize potential biological effects of specific impurities may not be necessary, however, if the manufacturing process used to produce the proposed product introduces different impurities or higher levels of impurities than those present in the reference product, additional pharmacological/toxicological or other studies may be necessary.

- To obtain sufficient information of the product-related substances and impurities it is recommended that comparative stability studies under accelerated and/or stress conditions are conducted - Process-related impurities arising from cell substrates (e.g., host cell DNA, host cell proteins), cell culture components (e.g., antibiotics, media components), and downstream processing steps (e.g., reagents, residual solvents, leachable/extractable , endotoxin, bioburden) should be evaluated.

- The process-related impurities in the proposed product are not expected to match those observed in the reference product and are not included in the comparative analytical assessment. Nevertheless, State-of-the-art analytical technologies following existing guidelines and compendial requirements should be applied, and the potential risks related to these newly identified impurities (for example, immunogenicity) have to be appropriately documented and justified.

- The chosen analytical procedures should be adequate to detect, identify, and accurately quantify biologically significant levels of impurities. In particular, results of immunological

methods used to detect host cell proteins depend on the assay reagents and the cell substrate used. Such assays should be validated using the product cell substrate and orthogonal methodologies to ensure accuracy and sensitivity.

7.8. Comparative analytical assessment

7.8.1 General Principle

- An extensive head-to-head comparability exercise will be 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 sensitive and orthogonal methods to determine not only similarities but also potential differences in quality attributes. Any differences detected in the quality attributes will have to be appropriately justified with regard to their potential impact on safety and efficacy.
- The aim of the biosimilar comparability exercise is to demonstrate that the biosimilar product and the RP chosen by the applicant are similar at the level of the finished medicinal product as well as adequate characterization of the proposed product and understanding of manufacturing variability.
- Demonstration of similarity of a biosimilar to an RP in terms of structural and functional aspects is a prerequisite for establishing comparability, with a tailored clinical data package required as needed.
- A clinical bioequivalence trial with pharmacokinetic (PK) and pharmacodynamic (PD) parameters (if available), and including an assessment of immunogenicity in human subjects, will typically be a core part of the clinical comparability assessment, unless scientifically justified.
- Complete CMC data in CTD format according to ICH guidelines, preclinical and clinical comparative studies with the same reference product used in the quality comparability *exercise should be submitted.*
- The decision to register a biosimilar should be based on evaluation of the whole data package generated during the overall comparability exercise.
- If relevant differences between the proposed biosimilar and the RP are detected at any stage (structural, functional, nonclinical or clinical level) the reasons should be justified. If this is not possible, the product is unlikely to qualify as a biosimilar and a full registration(standalone) application should be considered.

7.8.2 Biosimilarity principles

- Characterization of the quality attributes of the RP should be the first step in guiding the development of the biosimilar. The subsequent comparability exercise should demonstrate structural, functional, stability and clinical similarity.
- Development of biosimilar product together with proving biosimilarity relies on the manufacturer of the drug product, whether the drug substance manufacturer is the same entity of the drug product manufacturer or a contract manufacturer. If the manufacturer of the drug substance differs from that of the drug product, it will be the applicant's responsibility to provide the regulatory authority with the active substance full data within CTD either by his own submission or directly by the manufacturer of the active substance.
- The manufacturing process of the biosimilar should be developed based on a comprehensive understanding of the RP gained through detailed characterization studies of a sufficient number of RP batches (at least three batches of RP).

- It's recommended for the applicant during development process to monitor all the data regarding the safety and efficacy of the reference product.
- A sufficient number of RP batches and biosimilar batches (preferably representative of the material intended for commercial use) should be evaluated. Assay and batch to-batch variability will affect the number of batches needed. The number tested should be sufficient to draw meaningful conclusions on the variability of a given parameter for both the biosimilar and the RP and on the similarity of both products.
- Particular attention should be given to critical quality attributes that might have an impact on immunogenicity or potency, or that have not been identified in the reference medicinal product.
- The use of enhanced approaches to pharmaceutical development, along with quality risk management, effective quality systems and implementing good manufacturing practices, will facilitate the consistent manufacturing of a high-quality product.
- A biosimilar is manufactured and controlled according to its own development, taking into account state-of–the-art information on manufacturing processes and consequences on product characteristics.
- A comprehensive understanding of all steps in the manufacturing process for the proposed product should be established during product development. Information gained during process development including characterization tests, process controls and specifications must be specific for the proposed product and manufacturing process.
- Molecular characteristics and Quality Attributes (QA) of the target product profile should be comparable to the reference medicinal product; The Quality Target Product Profile (QTPP) of a biosimilar should be based on data collected on the chosen RP, including publicly available information and data obtained from extensive characterization of different batches of the RP. Since The biosimilar medicinal product is defined by the molecular composition of the active drug substance resulting from its manufacturing process, which may introduce its own molecular variants, isoforms or other product-related substances as well as product and process related impurities. As a consequence, the manufacturing process should be appropriately designed to achieve the QTPP. Performance and Consistency of the manufacturing process of the biosimilar on its own.

7.8.3 Considerations for the RP and the biosimilar

- The number of RP batches needed for the comparative analytical assessment will be influenced by the criticality of the quality attribute(s) under investigation and the approach chosen for demonstrating similarity. The manufacturer of the biosimilar should include an appropriate and scientifically supportable number of batches of the RP in the comparability assessment. In order to characterize independent RP batches, it is recommended that the RP batches are sourced over an extended time period. These batches should also include the RP batches used in the clinical comparison studies of the biosimilar.
- In general, sampling a higher number of RP batches will provide a better estimate of the true batch-to-batch variability of the RP and allow for a more robust statistical comparison with the biosimilar. Random sampling of RP batches is desirable but may be difficult to achieve in practice depending on the availability of such batches.
- However, the sourcing of RP batches should be carefully managed to generate a sample that captures the inherent variability of the RP (for example, collected over a sufficient time frame with the aim of covering different manufacturing campaigns).
- The RP batches should be transported and stored under the recommended conditions and tested within their approved shelf-life. Any exception to this would have to be fully

substantiated with experimental data.

- The shelf-life of the RP at time of characterization should be considered and it is expected that RP batches of different ages will be included in the similarity assessment.
- The biosimilar batches included in the comparability assessment should be manufactured using the intended commercial manufacturing process and should preferably originate from different drug substance batches.
- Generally, each value for an attribute being assessed for a biosimilar should be contributed by an independent batch. For example, a single drug product batch produced from a single drug substance batch would be considered to be an independent batch while different drug product batches produced from the same drug substance batch cannot be considered to be independent.
- In addition, small- or pilot-scale batches can be included if comparability between the small- and commercial scale batches has been properly demonstrated. Usually all commercial-scale batches produced – including process performance qualification batches and batches applied in the clinical trial(s) – should be included in the similarity assessment. As with the RP, the exact number of biosimilar batches required will be influenced by several factors, such as the criticality of the quality attribute(s) under investigation and the approach applied for similarity evaluation.
- In general, the risk of a false-positive conclusion on similarity will decrease with increasing number of batches. A robust manufacturing control system and demonstrated batch-to-batch consistency of the biosimilar (see section 7.2 above) are prerequisites for a successful similarity assessment.*(7)*

7.8.4 Considerations for similarity assessment

- Prior to initiating the comparability exercise, it is recommended that the quality attributes of the RP are identified and ranked according to their impact on the clinical performance of the product. For this purpose, a risk ranking tool could be developed. Such risk ranking tools should consider the impact of the quality attribute on safety, efficacy, PK and immunogenicity.
- Furthermore, the degree of uncertainty of impact should be taken into consideration. If it is known that a quality attribute will impact the clinical performance (that is, the uncertainty is low but the impact high) then that quality attribute should be prioritized and the overall risk score should be high. In cases where the clinical relevance of a certain quality attribute is unknown (that is, the uncertainty is high) then higher risk scores should be assigned even to lower impact quality attributes.
- The result of the risk ranking could then be used to guide the data analyses and the overall assessment of similarity. The most frequently used approach for similarity assessment relies on demonstrating that the quality attributes of the biosimilar batches lie within the predetermined similarity ranges established based on characterization data from multiple batches of the RP. Other approaches (such as equivalence testing of means) can also be used for similarity assessment.
- Each statistical approach has, however, specific strengths and weaknesses which should be appropriately discussed in the submission and considered in the similarity conclusion.
- In order to mitigate the risks inherent in employing statistical tests on limited sample (false-positive and false-negative conclusions), a comprehensive control strategy must be established for the biosimilar to ensure consistent manufacturing.

7.9. Specifications

- Specifications are critical quality standards that are proposed and justified by the

manufacturer and approved by regulatory authorities as conditions of approval to ensure product quality and consistency. They should focus on those molecular and biological characteristics found to be useful in ensuring the safety and efficacy of the product.

- The selection of tests to be included in the specifications is product specific and should be performed according to the ICH guidelines Q6B.
- Specifications for a biosimilar may not be the same as for the RP since the manufacturing process will be different and different analytical procedures and laboratories will be used for the assays. Nonetheless, the specifications should capture and control important known product quality attributes.
- Each acceptance criterion should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, and by data from lots used for the manufacturing process validation, data from stability studies, relevant development data and data obtained from the quality, safety and efficacy comparability exercise. The setting of specifications should be supported by global reasoning based on the manufacturer experience of the biosimilar product (quality, safety and efficacy) and own experimental results obtained by testing the reference product.
- Methods used for setting specifications may or may not be the same as analytical methods used for product characterization and for establishing product comparability.
- The setting of specifications should be based on:

- The manufacturer's experience with the biosimilar (for example, with regard to its manufacturing history, assay capability and the quality profile of batches used for establishing similarity).
- The experimental results obtained by testing and comparing the biosimilar and RP.
- Attributes with potential impact on product performance.
- Available monograph (Where this exist)
- The manufacturer should take into consideration that the limits set for a given specification should not, unless properly justified, be significantly wider than the range of variability of the RP over the shelf-life of the product.

7.10. Formulation / Container closure system

- The formulation of the biosimilar should be selected taking into account state-of-the-art technology and, regardless of the formulation selected, the suitability of the proposed formulation with regards to stability, compatibility (i.e., interaction with excipients, diluents and packaging materials), integrity, activity and strength of the active substance should be demonstrated.
- Sponsors should clearly identify excipients used in the proposed product that differ from those in the reference product. The acceptability of the type, nature, and extent of any differences between the finished proposed product and the finished reference product should be evaluated and supported by appropriate data and rationale.
- Additionally, different excipients in the proposed product should be supported by existing toxicology data for the excipient or by additional toxicity studies with the formulation of the proposed product.
- Excipient interactions as well as direct toxicities should be considered. The acceptability of the type, nature, and extent of any differences between the proposed finished biosimilar product and the finished reference product should be evaluated. Proteins are very sensitive to their environment. Therefore, differences in excipients or primary packaging may affect product stability and/or clinical performance.

- Differences in formulation and primary packaging between the proposed product and the reference product are among the factors that may affect whether or how subsequent clinical studies may take a selective and targeted approach.
- If a different formulation and/or container/closure system to the RP is selected (including any material that is in contact with the medicinal product), its potential impact on the safety and efficacy should be appropriately justified.*(7)*

7.11. Stability

- Stability studies should be summarized in an appropriate format (such as tables) and should include results from accelerated degradation studies and studies under various stress conditions for example: high temperature, oxidation, freeze-thaw, light exposure, humidity and mechanical agitation or as per nature of the product .
- The stability data should support the conclusions reached on the recommended storage and shipping conditions and on the shelf life and storage period for the drug substance, drug product and process intermediates which might be stored for significant periods of time.
- Stability studies should be carried to show which release and characterization methods are stability indicating for the product.
- Real time/real temperature stability studies should be performed to determine the storage conditions and shelf life for the biosimilar (which may or may not be the same as those for the RP). Results from studies conducted under accelerated and stress conditions may also show that additional controls should be used in the manufacturing process, and during shipping and storage, in order to ensure the integrity of the product.
- Comparative stability studies conducted under accelerated, and/or in some cases stress conditions (for example, freeze-thaw, light exposure and mechanical agitation), can be valuable in determining the similarity of the products by showing a comparable degradation profile and rate, with formulation, volume, concentration and/or container differences taken into account.
- Stability studies on both drug substance and drug product should be carried out using containers and conditions that are representative of the actual storage containers and conditions.
- Drug Product with different container orientations should be included in the stability study to evaluate potential impact of protein/container interactions.
- Typically, vials are stored in both inverted and upright positions while syringes are stored horizontally.
- At time of submission, stability data is on at least 3 lab or pilot scale batches can be provided with a commitment to place the first 3 manufacturing scale batches into the long-term stability program after approval.
- Any claims with regard to stability and compatibility cannot be extrapolated from the reference product and must be supported by data. Data should be collected for such orientations early in product development and potentially can be used to justify the use of worst-case scenarios only for later studies
- The minimum sterility testing generally performed as a component of stability protocol for sterile products is at initial time point (release) and final testing interval (expiration).
- Alternatives to sterility testing as part of stability protocol such as replacing the sterility test with container closure integrity. Container closure integrity can replace sterility testing as a part of sterility protocol.*(7)*

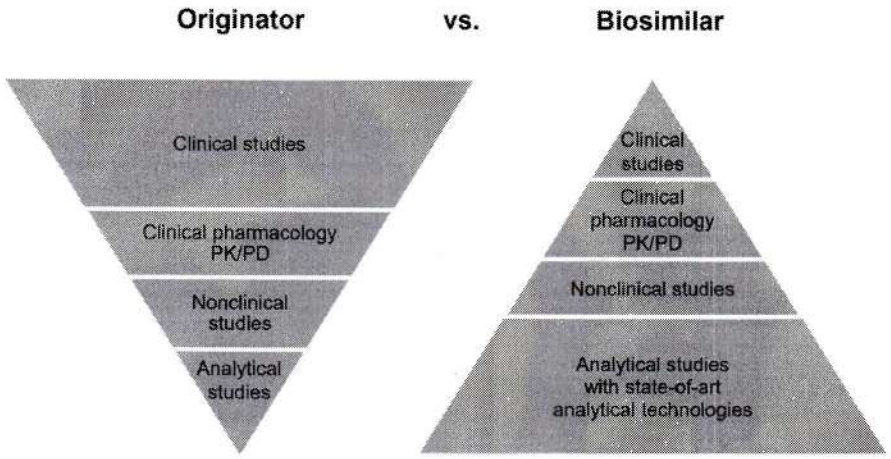
8. Non-clinical evaluation

This section addresses the pharmaco-toxicological assessment of the biosimilar. It is important to note that in order to design an appropriate nonclinical study programme a clear understanding of the characteristics of the RP is required.

The nature and complexity of the RP will have an impact on the extent of the nonclinical studies needed to confirm biosimilarity. In addition, any differences observed between the biosimilar and RP in the physicochemical and biological analyses will also guide the planning of the nonclinical studies. Other factors that need to be taken into consideration include the mechanism(s) of action of the drug substance (for example, the receptor(s) involved) in all authorized indications of the RP, and the pathogenic mechanisms involved in the disorders included in the therapeutic indications.

A stepwise approach should be applied during nonclinical development to evaluate the similarity of the biosimilar and its selected RP. At first, in vitro studies should be conducted and then a decision made on whether or not additional in vivo animal studies are required.

The following approach to nonclinical evaluation may be considered and should be tailored on a case-by-case basis to the biosimilar concerned. In all cases, the approach chosen should be scientifically justified in the application dossier.



(ref: Modified from Berghout A. Biologicals. 2011;39:293-6; McCamish M. Presented at EMA Workshop on Biosimilars, London, October 2013; and MacDonald J. APEC Biotherapeutics Workshop, Seoul, 2013)

Figure: Relative Effort in Development Pathway *(8)*

8.1. In vitro studies

Assays, such as receptor-binding studies or cell-based assays cell-proliferation, should normally be undertaken in order to establish the comparability of the biological/ pharmacodynamics activity of the biosimilar product and the reference product. Such data are usually already available from the biological assays of the quality evaluation. These studies may be referenced in the non-clinical evaluation.

In order to assess any relevant difference in pharmaco-toxicological activity between the biosimilar and chosen RP, data from a number of comparative in vitro studies – some of which may already be available from the quality-related assays – should be provided. In light of this data overlap, it is suggested that the in vitro nonclinical studies related to characterization of

the biological activity of the biosimilar be addressed alongside the related quality data in the corresponding quality module (see section 7.3.2 above). Any other nonclinical in vitro studies should then be addressed in the relevant nonclinical modules of the dossier where they should be reviewed and discussed from the point of view of potential impact on the efficacy and safety of the biosimilar.

Since experience has shown that in vitro assays are in general more specific and sensitive than in vivo studies in animals for detecting differences between the biosimilar and RP, the use of in vitro assays is of paramount importance in the nonclinical biosimilar comparability exercise.

- Typically, a battery of interaction studies addressing the primary binding events should be performed, along with cell-based or isolated-tissue-based functional assays (see below) in order to assess if any (clinically) relevant differences in reactivity exist between the biosimilar and RP and, if so, to determine the likely causative factor(s).
- Together, these assays should cover the whole spectrum of pharmaco-toxicological aspects with potential clinical relevance for the RP and for the product class. In the dossier, the manufacturer should discuss to what degree the in vitro assays used can be considered representative/predictive of the clinical situation according to current scientific knowledge.
- The studies should be comparative and designed to be sufficiently sensitive, specific and discriminatory to allow for the detection of (clinically) relevant differences in pharmaco-toxicological activity between the biosimilar and RP – or, conversely, to provide evidence that any observed differences in quality attributes are not clinically relevant.
- The studies should compare the concentration–activity/binding relationship of the biosimilar and the RP at the pharmacological target(s), covering a concentration range within which potential differences are most accurately detectable (that is, the ascending part of the concentration–activity/binding curve).
- A sufficient number of RP batches and biosimilar batches (preferably representative of the material intended for commercial use) should be evaluated. Assay and batch- to-batch variability will affect the number of batches needed. The number tested should be sufficient to draw meaningful conclusions on the variability of a given parameter for both the biosimilar and the RP and on the similarity of both products (see section 7.4.1 above).
- Where available, international reference standards can be used to support assay characterization, calibration and performance (see section 7.1 above). When no such reference standard exists, an in-house reference material should be established.
- The nonclinical in vitro programme for biosimilars should usually include relevant assays for binding studies.

If the quality and nonclinical in vitro comparability exercises indicate relevant differences between the biosimilar and the RP (thus making it unlikely that biosimilarity would eventually be established), then standalone development to support a full marketing authorization application should be considered instead (see section 5 above).

8.2. Determination of the need for in vivo animal studies

On the basis of the totality of quality and nonclinical in vitro data available and the extent to which there is residual uncertainty about the similarity of a biosimilar and its RP, it is at the discretion of the DGDA to waive or not to waive a requirement for additional nonclinical in vivo animal studies. The decision on whether or not to require such studies should take into account the following:

- If the quality comparability exercise and the nonclinical in vitro studies have shown high similarity and the level of residual uncertainty is considered acceptable to move to the clinical phase of the similarity exercise then an additional in vivo animal study is not considered necessary.

- If a need is identified to reduce remaining uncertainties concerning the similarity (including drug safety) of a biosimilar and its RP before the initiation of clinical evaluations then additional in vivo animal studies may be considered, if a relevant animal model is available – however this should only occur:
- when it is expected that such studies would provide relevant additional information; and
- if the needed additional information cannot be obtained using an alternative approach that does not involve in vivo animal studies. In this respect, the factors to be considered could include:

- qualitative and/or quantitative differences in potentially or known relevant quality attributes between the biosimilar and its RP (for example, qualitative and/or quantitative differences in the post-translational glycosylation of proteins); and
- relevant differences in formulation (for example, use of excipients in the biosimilar not widely used in medicinal products).

- On the basis of regulatory experience gained to date in marketing authorization applications for biosimilars, the need for additional in vivo animal studies would be expected to represent a rare scenario.
- If the quality and nonclinical in vitro comparability exercises indicate relevant differences between the biosimilar and the RP, then standalone development to support a full marketing authorization application should be considered instead.

8.3. In vivo studies

8.3.1. General aspects to be considered

In the exceptional case that an in vivo evaluation is deemed necessary by DGDA, the focus of the study/studies (PK and/or PD and/or safety) will depend upon the type of additional information needed.

Animal studies should be designed to maximize the information obtained. The 3Rs principles for animal experiments (Replace, Reduce, Refine) should always be followed to minimize the use of animals in testing.

To address the residual uncertainties, the use of conventional animal species and/or of specific animal models (for example, transgenic animals or transplant models) may be considered.

Animal models are often not sensitive enough to detect small differences. If a relevant and sufficiently sensitive in vivo animal model cannot be identified, the manufacturer may choose to proceed directly to clinical studies, taking into account strict principles to mitigate any potential risk.

The effects of RPs are often species specific. In accordance with ICH S6(R1) *(9)* and the WHO Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology *(1)*, in vivo studies should be performed only in relevant species – that is, species which are known to be pharmacologically and/or toxicologically responsive to the RP.

The duration of the study/studies should be justified, taking into consideration the PK behaviour of the RP, the time to onset of formation of anti-drug antibodies (ADAs) in the test species and the clinical use of the RP.

8.3.1 Specific aspects

8.3.1.1 PK and/or PD studies

In cases where such studies are considered necessary, the PK and/or PD of the biosimilar and the RP should be compared quantitatively, when the model allows, using a dose–response assessment that includes the intended exposure in humans.

The studies may include animal models of disease to evaluate functional effects on disease-related PD markers or efficacy measures.

8.3.1.2 Safety studies

Where in vivo safety studies are deemed necessary, a flexible approach that follows the 3R principles to maximize the readout of relevant data and minimize the use of animals in testing should always be followed. If appropriately justified, a repeated dose toxicity study with refined design – for example, using just one dose level of biosimilar and RP, and/or just one gender and/or no recovery animals, and/or only in-life safety evaluations such as clinical signs, body weight and vital functions – may be considered. Depending on the chosen end-points, it may not be necessary to sacrifice the animals at the end of the study.

Repeated dose toxicity studies in non-human primates are not recommended and nor are toxicity studies in non-relevant species (for example, to assess unspecific toxicity due to impurities).

8.3.1.3 Immunogenicity studies

Qualitative or quantitative difference(s) in product-related variants (for example, in glycosylation patterns, charge, aggregates, and impurities such as host-cell proteins) may have an effect on immunogenic potential and on the potential to cause hypersensitivity. These effects are usually difficult to predict from animal studies and are better assessed in clinical studies.

However, determination of antibody formation against the study drugs may be required for the interpretation of PK/toxicokinetic data in cases where in vivo animal studies are needed.

8.3.1.4 Local tolerance studies

Studies on local tolerance are usually not required. However, if excipients are introduced for which there is little or no experience with the intended clinical route of application, local tolerance may need to be evaluated. If other in vivo animal studies are to be conducted, the evaluation of local tolerance may be integrated into the design of those studies.

8.3.1.5 Other studies

In general, safety pharmacology and reproductive and development toxicity studies – as well as genotoxicity and carcinogenicity studies; see *(1)* and *(9)* – are not warranted during the nonclinical testing of biosimilars.

9. Clinical Evaluation

The main clinical data should be generated using the biosimilar product derived from the final manufacturing process, and which reflects the product for which marketing authorization is being sought. Any deviation from this recommendation needs to be justified and additional data may be required. For changes in the manufacturing process, relevant guidelines should be followed. Ideally, an RP from a single marketing authorization holder would be used as the comparator throughout the comparability programme of quality and clinical studies during the evaluation of the biosimilar in order to allow for the generation of coherent data and conclusions. Clinical studies are a valuable step in confirming similarity. The goal of such studies is to confirm the absence of any clinically relevant differences between the proposed biosimilar and the RP. Clinical studies should be designed to demonstrate confirmative evidence of the similar clinical performance of the biosimilar and the RP, and therefore need to

use testing strategies that are sufficiently sensitive to detect any clinically relevant differences between the products.

If relevant differences between the biosimilar and the RP are detected at any stage of development, the reasons will need to be explored and justified. If this is not possible, the new product may not qualify as a biosimilar and a full Registration or Marketing Authorization (standalone) application should be considered.

A comparative bioequivalence study involving PK and/or PD comparability is generally required for clinical evaluation. An adequately powered comparative efficacy and safety trial will not be necessary if sufficient evidence of biosimilarity can be drawn from other parts of the comparability exercise. The need for a comparative clinical efficacy and safety trial for the proposed biosimilar (and type of trial if required) will be influenced by factors such as:

- how well the biosimilar can be characterized;
- the availability of suitable, sensitive and orthogonal assays for adequate analytical and functional characterization;
- the degree of analytical and functional similarity between the biosimilar and RP;
- the existence of a relevant PD parameter;
- the degree of understanding of the mechanism(s) of action of the biological product in different indications and how well these can be investigated in binding and functional in vitro tests – the contribution of each mechanism of action to the observed clinical effect is not relevant as long as it can be measured;
- knowledge of any (potentially) unwanted immunogenicity – for example, ADA incidence and the magnitude of ADA response including level of neutralizing antibodies, and antibodies targeting endogenous substances (for example, erythropoietin and coagulation factors); and
- Whether the impurity profile or the nature of excipients of the biosimilar gives rise to clinical concerns. Current examples of biological products that can be comprehensively characterized and have a well-established mechanism of action include (but are not limited to) teriparatide, insulin, G-CSF and somatropin (10, 11). The current data suggest that more-complex products such as mAbs can be sufficiently characterized by available suitable analytical methods, plus the structure–function relationships are well known and can be studied by sensitive orthogonal functional assays.

9.1. Pharmacokinetic studies

The clinical comparability exercise should generally include a comparative PK study, if the drug substance can be measured in the blood, and should also include the measurement of PD markers if available and also immunogenicity data. The PK study should be designed to demonstrate similar PK profiles for the biosimilar and the RP. When the RP and its proposed biosimilar have more than one route of administration (most commonly intravenous and subcutaneous) then carrying out the study/studies using the non-intravenous route of administration is preferred as this is usually the more immunogenic route and will provide more meaningful information for the comparability exercise.

The omission of a PK study of other approved routes of administration needs to be justified for approval of all available options – for example, in cases when the molecule has an absorption constant that is much lower than the elimination constant (flip flop kinetics).

The sample size should be appropriate, taking into account PK variability in the study population, and consideration should be given to whether a cross-over or parallel group design would be the most adequate. If appropriate population PK or PK-PD models are available for the RP in the literature, modelling and simulation can be considered for optimizing study

design – for example, justification of dose(s) and selection of the most sensitive study population to detect potential PK differences, and choice of sample size.

PK studies should preferably be performed in healthy volunteers (if considered ethical) and care should be taken to standardize the population with regard to factors that may influence variability (for example, ethnic origin, body weight and gender). If the drug substance under investigation is associated with risks or tolerability issues that are considered to be unacceptable for healthy volunteers, it will be necessary to perform the PK studies in patients.

The preferred design is a randomized, two-period, two-sequence, single dose cross-over PK study using a dose within the therapeutic range at which the ability to detect differences is sufficient to observe meaningful differences. The cross-over design eliminates inter-subject variability and therefore (compared with the parallel group design) reduces the sample size needed to show equivalent PK profiles of the biosimilar and RP. The treatment periods should be separated by a wash out phase that is sufficiently long to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period – that is, at least 5 times the terminal half-life. When a cross-over design is not suitable (for example, for biological products with a very long half-life or associated with immunogenicity affecting PK) then a parallel group study should be considered. In parallel group studies, care should be taken to avoid any imbalances between treatment groups that might affect the PK of the drug substance under investigation (for example, with regard to ethnic origin, body weight and gender).

A multiple-dose study in patients is acceptable as a pivotal PK study if a single-dose study cannot be conducted in healthy volunteers due to risks or tolerability reasons or if a single-dose study is not feasible in patients. Multiple dose studies may also be acceptable in rare situations where problems with the sensitivity of the analytical method preclude sufficiently precise plasma or serum concentration measurements after a single dose administration. However, given that a multiple-dose study is less sensitive in detecting differences in Cmax than a single-dose study, this will only be acceptable with sound justification. PK comparison of the biosimilar and the RP should not only include the rate and extent of absorption but also a descriptive analysis of elimination characteristics – that is, clearance and/or elimination half-life – which might differ between the biosimilar and the RP. Linear (nonspecific) clearance and nonlinear (target-mediated) clearance should be evaluated by assessment of partial areas under the curve (pAUCs). For further details on primary and secondary end points for single- and multiple-dose PK studies, please refer to further guidance documents (13).

Acceptance criteria for the demonstration of PK similarity between the biosimilar and the RP must be predefined and appropriately justified. It should be noted that the criteria used in standard clinical PK comparability studies (bioequivalence studies) may not necessarily be applicable to all biotherapeutic products. However, the traditional 80–125% equivalence range will in most cases be sufficiently conservative to establish similar PK profiles (24). Correction for protein content may be acceptable on a case-by-case basis if pre-specified and adequately justified, with the assay results for the biosimilar and RP being included in the protocol. If adjustments for covariates are intended for parallel group studies (for example, in the case of adalimumab, stratification for body weight and gender), they should be predefined in the statistical analysis plan rather than being included in post hoc analyses.

Other PK studies, such as interaction studies (with drugs likely to be used concomitantly) or studies in special populations (for example, children, the elderly and patients with renal or hepatic insufficiency), are not required for a biosimilar.

Particular consideration should be given to the analytical method selected and its ability to detect and follow the time course of the protein in a complex biological matrix that contains many other proteins. The method should be optimized to provide satisfactory specificity, sensitivity and a range of quantification of adequate accuracy and precision. The same assay should be used to detect the serum concentrations of both the biosimilar and RP.

A single PK assay (same binding reagents and a single analytical standard, usually a biosimilar) for determining biosimilar and RP concentration in a biological matrix can be adopted based on verification of the bioanalytical comparability of the two products within the method, with supporting data (14).

In some cases, the presence of measurable concentrations of endogenous protein may substantially affect the measurement of the concentration–time should describe and justify the approach taken to minimize the influence of the endogenous protein on the results (for example, baseline correction).

In some cases, it may not be possible or meaningful to establish PK similarity due to the nature of the substance (for example, fractionated and unfractionated heparin cannot be measured in blood), the route of administration (for example, intraocular administration of aflibercept or ranibizumab) or unacceptably high PK variability (for example, romiplostim). In such cases clinical similarity should be supported by PD, immunogenicity and/or other clinical parameters.

9.2. Pharmacodynamic studies

PD parameters should preferably be investigated as part of the comparative PK studies. In some cases, PK studies cannot reasonably be conducted and PD markers may then play a more important role. This is for example the case with heparins,19 where serum concentrations cannot be measured and similarity needs to be established for the most important PD end-points; that is, at least anti-FXa and anti-FIIa activity.

PD effects should be investigated in a suitable population using a dose or doses within the steep part of the dose–response curve in order to maximize the chance of detecting potential differences between the biosimilar and the RP. PD markers should be selected on the basis of their clinical relevance.

9.3. Confirmatory PK and/or PD studies

If an adequately powered comparative efficacy trial is not necessary, comparative PK (see section 9.1 above) and/or PD studies (see section 9.2 above) may be sufficient for establishing confirmative evidence of the similar clinical performance of a biosimilar and its RP, provided that

- the acceptance ranges for confirmatory PK and/or PD end-points are predefined and appropriately justified;
- the PD biomarker reflects the mechanism of action of the biological product;
- the PD biomarker is sensitive to potential differences between the proposed biosimilar and the RP; and
- the PD biomarker assay is validated. The applicant should consider the option of using additional PD measures (usually as secondary end-points) to assess the comparability of the PD properties is not available, sensitive PD end-points may be assessed if such assessment may help to reduce residual uncertainty about biosimilarity.

An example of acceptable confirmatory PK/PD studies would be the use of euglycaemic clamp studies to compare the efficacy of two insulins. In addition, absolute neutrophil count and CD34+ cell count are the relevant PD markers for assessing the activity of G-CSF and could be used in PK/PD studies in healthy volunteers to demonstrate the similar efficacy of two medicinal products containing G-CSF.

The study population and dosage should represent a test system that is known to be sensitive in detecting potential differences between a biosimilar and the RP. In the case of insulin, for example, the study population should consist of non-obese healthy volunteers or patients with

type 1 diabetes rather than insulin-resistant obese patients with type 2 diabetes. Otherwise, it may be necessary to investigate more than one dose to demonstrate that the test system is discriminatory.

The acceptance ranges for confirmatory PK and/or PD parameters (that is, for primary end-points) should be predefined and appropriately justified. If PD comparison is not essential for a conclusion of biosimilarity but the results are still expected to reasonably support biosimilarity then a purely descriptive analysis of the PD results may be justified. This may be the case for biological substances that have been extensively characterized and for which biosimilarity can already be concluded from the analytical, functional and PK comparisons.

If appropriately designed and performed, such PK/PD studies are usually more sensitive in detecting potential differences in efficacy than trials using hard clinical end-points.

However, PD markers may also be used as end-points in clinical efficacy studies in patients. Examples of appropriate markers include haemoglobin for measuring the efficacy of an epoetin, and lactate dehydrogenase (which is a sensitive biochemical marker of intravascular haemolysis) for evaluating the efficacy of a complex drug such as eculizumab. For denosumab, investigation of bone formation and resorption markers as part of the PK study may be useful or possibly sufficient. This would involve measurement of bone mineral density and bone turnover markers such as serum C-terminal telopeptide of type 1 collagen (CTX-1) and procollagen type 1 N-terminal propeptide (P1NP) after denosumab administration.

In certain cases (for example, when analytical similarity of the active ingredient in the biosimilar and the RP can be demonstrated to such a degree that clinical differences can be excluded) a comparative PK study may provide sufficient clinical evidence to support biosimilarity. However, a risk assessment (including for example, the impurity profile) should be conducted to determine the need for additional safety/immunogenicity data on the biosimilar (see sections 9.5 and 9.6 below) *(15)*.

9.4. Efficacy studies

A comparative efficacy trial may not be necessary if sufficient evidence of biosimilarity can be inferred from other parts of the comparability exercise. A comparative clinical trial, if necessary, should confirm that the clinical performance of the biosimilar and the RP is comparable. Demonstration of comparable potency, PK and/or PD profiles provide the basis for use of the RP posology in the comparative clinical trial.

If a comparative clinical trial of the biosimilar and RP is deemed necessary then it is expected that it will be an adequately powered, randomized and controlled clinical trial performed in a patient population that allows for sensitive measurement of the intended clinical parameters. The principles of such trials are laid down in relevant ICH guidelines *(16–18)*.

In principle, equivalence trial designs (requiring lower and upper comparability margins) are preferred for comparing the efficacy and safety of the biosimilar and RP. Non-inferiority designs (requiring only one margin) *(16)* or trials with asymmetrical margins may be considered if appropriately justified *(19)*. Regardless of which design is selected in a particular case, the comparability margin(s) must be pre-specified and justified on the basis of clinical relevance – that is, the selected margin should represent the largest difference in efficacy that would not matter in clinical practice.

Treatment differences within this margin would therefore be acceptable as they would have no clinical relevance. Similar efficacy implies that similar treatment effects can be achieved when using the same posology, and the same dosage(s) and treatment schedule should be used in clinical trials comparing the biosimilar and RP.

In this regard, equivalence trials are again preferable to ensure that the biosimilar is not clinically less or more effective than the RP when used at the same dosage(s).

A non-inferiority design could be acceptable, if justified by the applicant, for example:

- for biological products with high efficacy (for example, a response rate of over 90%), making it difficult to set an upper margin; or
- in the presence of a wide safety margin. When using asymmetrical margins, the narrower limit should rule out inferior efficacy and the broader limit should rule out superior efficacy. The use of asymmetrical margins should be fully justified by the sponsor of the proposed biosimilar. Factors that would allow for the use of such margins in a clinical trial include:
- if the dose used in the clinical study is near the plateau of the dose– response curve; and there is little likelihood of dose-related adverse effects (for example, toxicity).

The final results obtained from the comparative clinical trial(s) along with comparative analytical, functional and PK data will determine whether the biosimilar and the RP can be considered to be clinically similar. If clinically relevant differences are found, a root cause analysis should be performed. If a plausible cause that is unrelated to the product (for example, inadvertent baseline differences between treatment groups despite randomization) cannot be found, the new product should not be considered to be similar to the RP.

Careful consideration should be given to the design of the comparative study/studies, including the choice of primary efficacy end-point(s). Studies should be conducted using a clinically relevant and sensitive end-point within an homogenous population that responds well to the pharmacological effects of the biological product of interest to show that there are no clinically meaningful differences between the biosimilar and RP. Clinical outcomes, surrogate outcomes (PD markers) or a combination of both can be used as primary end-points in biosimilar trials. The same study end-points used to establish the efficacy of the RP may be used because a large body of historical data would generally be available in the public domain for setting the comparability margin(s) and calculating the sample size. However, the primary end-point could be different from the original study end-point for the RP if it is well justified and relevant data are available to support its use as a sensitive end-point and its suitability for the determination of the comparability margin(s). A relevant PD end-point can be used as the primary end-point – for example, when it is a known surrogate of efficacy or when it can be linked to the mechanism of action of the product.

The primary or secondary end-points can also be analyzed at different time points compared to those used in clinical trials with the RP if these are considered to be more sensitive in capturing the pharmacological action(s) of the biological product – for example, adalimumab efficacy could be measured by responses at week 12 or 16 in addition to week 24.

The sample size and duration of the comparative clinical study should both be adequate to allow for the detection of clinically meaningful differences between the biosimilar and RP. When a comparative clinical trial is determined to be necessary then adequate scientific justification for the choice of study design, study population, study end-point(s), estimated effect size for the RP and comparability margin(s) should be provided and may be discussed with regulators in order to obtain agreement at least in principle prior to trial initiation.

9.5. Safety

Safety data should be captured throughout clinical development from PK/PD studies and also in clinical efficacy trials when conducted. Knowledge of:

- the type, frequency and severity of adverse events/reactions when compared with the RP;
- whether these are due to exaggerated pharmacological actions;
- the degree of analytical and functional similarity of the biosimilar and RP; and
- the presence of novel impurities and novel excipients in the biosimilar will all inform the type and extent of data required to characterize the safety profile of the biosimilar.

If the clinical programme for the biosimilar is limited to confirmatory PK/PD studies, this will need to be adequately justified and a risk assessment should be conducted to determine the need to obtain additional safety data for the biosimilar. For example, for insulin the most relevant safety issue is hypoglycaemia which can be attributed to its pharmacological action. Highly similar physicochemical characteristics and PK/PD profiles of the biosimilar and RP could provide sufficient reassurance that the risk of hypoglycaemia is also similar, obviating the need for further safety data. Similar examples are teriparatide, filgrastim or somatropin. The current data suggest that more complex products such as mAbs can be sufficiently characterized and also fall into this category (*12*).

If the biosimilar contains impurities that are not present in the RP (for example, because of the use of a novel expression system) then the generation of further safety data may be necessary, or scientific justification should be provided as to why such data are not needed. Manufacturers should consult with regulators when proposing a clinical programme solely relying on PK/PD studies.

As for all medicinal products, further monitoring of the safety of the biosimilar will be necessary in the post-marketing phase (see section 10 below).

9.6. Immunogenicity

Immunogenicity should be investigated as part of the clinical evaluation package of the biosimilar relative to the RP unless the manufacturer can provide a scientific justification that human immunogenicity data are not needed. Such justification should be based on the degree of physicochemical similarity of the biosimilar and RP, and on a thorough risk assessment of any unwanted immunogenicity and clinical consequences known for the RP. Although published information will be useful in gaining knowledge of the immunogenicity risk of the RP and in planning the immunogenicity strategy, it is not generally sufficient to support approval of the biosimilar. The goal of the immunogenicity programme is to exclude an unacceptable/marked increase in the immunogenicity of the biosimilar when compared with the immunogenicity of the RP and to generate descriptive data in support of biosimilar approval and its clinical use. If conducted, the immunogenicity study report should include data on antibody incidence, magnitude of ADA response and neutralization ability, whether antibodies are transient or persistent, and their impact on PK and clinical correlates (*20*).

The marketing authorization application should include an integrated immunogenicity summary comprising a risk assessment and, if appropriate, the results of testing using appropriately validated and characterized assays, along with details on the clinical study duration, sampling schedules and regimen, and the clinical immunogenicity assessment (*20–22*).

The immunogenicity studies should be tailored to each product and require a multidisciplinary approach taking into account both quality and clinical considerations. The risk assessment should include:

- accumulated information on the immunogenicity of the RP (that is, on the nature, frequency and clinical relevance of the immune response);
- Consideration of the quality aspects (including the nature and complexity of the drug substance, non-glycosylated/glycosylated, expression system, product- and process-related impurities, and aggregates);
- Consideration of excipients and container closure system, and stability of the product, route of administration, dosing regimen; and
- Consideration of patient- and disease-related factors (for example, immune competent/compromised and any concomitant immunomodulatory therapy).

Placing particular emphasis on any differences in product-related factors (for example, impurities arising from a novel expression system and/or novel excipients) that could modify

immunogenicity will be crucial in the risk assessment of the biosimilar. Importantly, consideration of the type of product is also a critical element of the risk assessment, with the risk being higher for a product that has an endogenous non-redundant counterpart (for example, epoetin). In such cases, special attention should be paid to the possibility of the immune response seriously affecting the endogenous protein and its unique biological function, with serious adverse effects. Real-time testing for neutralizing ADAs is recommended for epoetins (*23*) and other high-risk products (for example, enzyme replacement therapies and coagulation factors).

Conversely, for well-characterized biological substances (for example, insulin, somatropin, filgrastim, teriparatide), where an extensive literature and clinical experience indicate that immunogenicity does not impact upon product safety and efficacy, immunogenicity studies may not be necessary, provided that the biosimilar is highly similar to the RP and the risk-based evaluation indicates a low risk. This may also be applicable to other products, including mAbs. In such cases, manufacturers should consult with the regulatory authorities.Appropriate scientific justification for not conducting a safety/immunogenicity study should always be provided.

9.6.1 Immunogenicity testing

A multi-tiered approach comprising screening and confirmatory immunoassays that detect binding ADAs followed by assays which determine ADA magnitude and neutralization potential is generally necessary and deviation from this requires justification.

Information on current assays and formats and on their benefits and limitations, along with the interpretation of results, has been extensively reviewed (*23–26*). The manufacturer will need to justify the antibody-testing strategy and the choice of assays to be used. Attention should be given to the selection of suitable controls for assay validation and to the determination of cut off points for distinguishing antibody-positive from antibody-negative samples. Aspects relating to potential interference by matrix components, including the pharmacological target and the residual drug in the sample, are also important.

To mitigate such interference, corrective measures should be implemented. For example, for drug interference (which commonly occurs with samples taken from patients given mAbs) measures such as allowing time for clearance of the drug from the circulation prior to sampling, or incorporating steps for dissociating immune complexes and/or removal of the drug can be used. Care should be taken to ensure that the use of such measures does not compromise ADA detection or patient treatment.

Where required, comparative immunogenicity testing should be performed using the same assay format and sampling schedule. For immunogenicity assessment in new drug development, antibody testing is performed using the therapeutic given to the patient. In applying this concept to biosimilars, the development of screening assays with a similar sensitivity for the two patient groups (biosimilar and RP) within the same study is very challenging. Therefore, in the biosimilar scenario, relative immunogenicity is often assessed by using a single assay which employs the drug substance of the biosimilar as the antigen for sample testing for both groups. This approach allows for the detection of all antibodies developed against the biosimilar. The manufacturer should demonstrate the suitability of the method(s) used and provide data assuring that the method(s) measure ADA to the RP and to the biosimilar to a similar extent (*25*).

Neutralization assays reflecting the mechanism of action are usually based on the potency assay of the product. Non-cell ligand-based assays are relevant in cases where the therapeutic binds to a soluble ligand and inhibits its biological action. For products associated with high risk (for example, those with non-redundant endogenous homologs) and those for which effector functions are important, the use of functional cell-based bioassays is recommended. Where necessary, advice on the need for a neutralization assay and on the appropriate format to

use (cell-based, ligand-based or based on enzyme activity) may be sought from regulatory authorities.

Further characterization of antibodies (for example, isotype) should be conducted if considered clinically relevant, or in special situations (for example, the occurrence of anaphylaxis or use of certain assay formats), taking into account the immunogenicity profile of the RP. For example, if the RP does not elicit an IgE response it is unlikely that the biosimilar would elicit one if the same expression system is used. The retention of patient samples under appropriate storage conditions will be necessary for retesting in cases where technical problems occurred with the original assay.

9.6.2 Clinical evaluation

ADAs can affect the PK, PD, safety and/or efficacy of the administered product. The immunogenic risk of a biological is determined by the ADA incidence in the treated population and the magnitude of the unwanted clinical effect, and influences the benefit–risk balance of the therapeutic.

If human immunogenicity data are needed, they should be generated in a comparative manner throughout the clinical programme. The sensitive patient population (that is, the population with the highest likelihood of mounting an immune response) is preferred for investigating immunogenicity. For example, if an epoetin is licensed for the treatment of renal anaemia and for patients with chemotherapy-induced anaemia, the selection of patients with renal anaemia is advised. Comparative PK and/or PD studies should be designed to also collect immunogenicity data regardless of the population to be included (for example, healthy volunteers and patients). A PK/PD cross-over design is possible for immunogenicity testing but if the exposure time until the switch does not provide sufficient immunogenicity data, the sponsor must ensure that a sufficient number of patients are treated without cross-over – for example, by extending the cross-over study with two parallel treatment arms, or by proposing a separate immunogenicity study.

If ADAs are known to affect the PK of the RP then ADA rate and kinetics assessments could be performed along with assessment of their impact on PK through pre-specified subgroup analysis of ADA-negative and -positive subjects.

The observation period required for immunogenicity testing will depend on the expected time of antibody development and should be justified by the manufacturer. Sampling during immunogenicity testing should include baseline sampling (prior to treatment) for pre-existing antibodies, sampling during treatment and in some cases post-treatment, particularly if ADAs persist or areundetectable at earlier time points (due to immunosuppressive properties of the product or technical problems such as drug interference). The sampling schedule should be synchronized for evaluation of PK as well as for assessment of safety and efficacy to provide an understanding of the impact of antibodies on clinical outcome. Generally, for chronic administration, 6-month data are acceptable to exclude excessive immunogenicity, but in some cases a longer evaluation period may be appropriate pre-licensing to assess antibody incidence and possible clinical effects.

Furthermore, notable differences in immunogenicity between the biosimilar and RP would require further investigation of the underlying cause, and data and justification provided to support any claim that the difference noted was not clinically relevant. An analysis of the clinical impact of ADAs in both arms on PK, efficacy and/or safety should be performed through stratified analysis of ADA-negative and -positive subjects.

Any potential for the production of neutralizing antibodies against critical endogenous factors (for example, following epoetin administration) will necessitate clinical studies in patients.

As is the case with the RP, the biosimilar should also undergo robust post marketing surveillance that includes assessment of any serious adverse events related to immunogenicity.

9.6.3 Authorization of indications

The decision to authorize the requested indications will be dependent upon the demonstration of similarity between the biosimilar and RP. Once a biosimilar candidate has been shown to be highly similar to the RP in terms of analytical characteristics, biochemical and functional properties related to the MOA of the RP, all the indication granted to RP can be claimed by the biosimilar candidate without further justification, provided they are not protected by market exclusivity or patent (*27*).

For example, authorization of all indications may be obtained based on highly comparable functional data – for example, for biosimilars of mAbs such as infliximab and adalimumab if they show fully comparable activity (including ADCC, CDC, reverse signalling and apoptosis) both in terms of binding to soluble TNF and membranous TNF.

10. Pharmacovigilance

Following approval, DGDA considers a biosimilar to have its own life-cycle and there is no formal requirement to re-establish similarity to the RP when comparability exercises are conducted following manufacturing changes (*2*, 6). Both RP and biosimilar manufacturers are responsible for ensuring that their products remain safe and efficacious throughout their life-cycle by preventing significant changes to individual products. In this context, it is important to emphasize that the required safety data can be obtained only by having robust pharmacovigilance systems in place following Good Pharmacovigilance Practices (GVP) Guideline for Marketing Authorization Holders (MAHs) in Bangladesh that allow for the collection of product-specific data. Post marketing observational study on reasonable number of subjects shall have to be submitted to DGDA.

As with all medicinal products, further close monitoring of the safety and efficacy of a biosimilar in all approved indications, along with continued benefit–risk assessment, are necessary in the post-marketing phase. Any specific safety monitoring or risk-minimization measures imposed on the RP or product class should be incorporated into the pharmacovigilance plan for the relevant biosimilar unless a compelling justification can be provided to show that this is not necessary. Furthermore, participation in existing disease registries should be encouraged and is mandatory if also mandatory for the RP. Post-marketing safety reports should include all information on product safety received by the marketing authorization holder. The safety information must be evaluated in a scientific manner and this should include evaluation of the frequency and cause of adverse events.

The manufacturer should submit a pharmacovigilance plan describing a safety specification, pharmacovigilance activities and risk-minimization activities at the time of submission of the marketing authorization application or whenever a safety concern arises post-marketing. The principles of pharmacovigilance planning can be found in relevant guidelines such as ICH E2E (*28*). The safety specification should describe important identified or potential safety issues for the RP and for the substance class as well as any that are specific to the biosimilar. If there are any remaining uncertainties regarding the biosimilar – due for example to the use of a novel excipient or device – then these should be included in the pharmacovigilance plan and followed up post-marketing. At the time of marketing authorization, manufacturers must ensure that an appropriate pharmacovigilance system is in place. This includes the appointment of a qualified person responsible for pharmacovigilance, as well as the necessary infrastructure for the timely notification and assessment of adverse drug reactions in all countries where the product is marketed. After the marketing authorization has been granted, it is the responsibility of the DGDA to monitor closely the compliance of manufacturers with their marketing commitments, particularly with regard to their pharmacovigilance obligations as described here. In addition, as with all biological products, an adequate system for ensuring the specific identification of the biosimilar (that is, traceability) is essential. In addition to the international nonproprietary name (INN) (29) an adverse reaction report for any biological should also include all other

important indicators, including the proprietary (brand) name, manufacturer's name and lot number. The country of origin is not strictly required but the Marketing Authorization Holder (MAH) name is essential.

11. Labelling and prescribing information

The biosimilar should be clearly identifiable by a unique trade name together with the INN. From the perspective of WHO there is no specific INN nomenclature for biosimilars – that is, there is no part of an INN which indicates that a product is a biosimilar. Biosimilars are assigned INNs using the process and rules used for all biological products.

In many cases, the INN for a biosimilar is the same as that for its RP – for example, for G-CSF biosimilars that have used Neupogen as the RP, both the biosimilar and the RP have the INN "filgrastim" (*29*, *30*). Provision of the lot number/batch number is essential as it is an important part of production information and is critical for traceability whenever problems with a product are encountered.

The prescribing information for a biosimilar should be as similar as possible to that of the RP except for product-specific aspects such as use of different excipient(s) and/or presentations. This similarity is particularly important for posology and for safety-related information, including contraindications, warnings and known adverse events.

12. Annexures

Annexure 1

❖ **Registration process flow for Biosimilar Products manufactured by imported bulk**

1. Application for NOC to import samples for R&D

2. Application for Source Validation

- ✓ Applicant will apply to DGDA for source validation as per the Drug and Cosmetics Act, 2023 section 42 with CTD Dossier format.
- ✓ CTD Dossier must be consists of 05 modules-
  - a) Module–1(Administrative and Prescribing Information)
  - b) Module–2(Quality Overall Summary)
  - c) Module–3 (Quality)
  - d) Module–4(Preclinical Study Report)
  - e) Module–5(Clinical Study Report)
- ✓ Screening and evaluation of Dossier
- ✓ Approval of source after satisfactory report.

3. Application for Registration of Biosimilar Products:

- ✓ Applicant will apply to DGDA for registration as per the Drug and Cosmetics Act, 2023 section 22 at front desk
- ✓ Applicant will apply with CTD Dossier format after getting source validation letter in both offline and online.
- ✓ CTD Dossier must be consists of 05 modules-
  - a) Module–1(Administrative and Prescribing Information)
  - b) Module–2(Quality Overall Summary)
  - c) Module–3 (Quality)
  - d) Module–4(Preclinical Study Report)
  - e) Module–5(Clinical Study Report)
- ✓ Application and receiving product sample at NDCL.
- ✓ Applicant will propose a brand name and the proposed brand name will be checked by MA department at DGDA database and applicant will receive a brand name of the product.
- ✓ Screening, Evaluation of Dossier and Moderator's comment
- ✓ After satisfactory evaluation report from MA, CT, PV and Lab, Head of MA will forward the report to DG, DGDA for approval along with the file & registration

approval letter.

- ✓ If Reports found satisfactory, DG, DGDA will sign the registration approval letter.
- ✓ Applicant will receive approval letter.

4. Application for Packaging Material (SmPC, PIL etc.) Approval

5. Application for Issuance of Price certificate

6. Application for Issuance of MA certificate

7. Post Marketing Documents need to submit at DGDA

✓ Submission of stability data of first 3 manufacturing scale batches into the long-term stability program

✓ Phase-iv observational study on reasonable number of subjects for 6 months to 1 year.

✓ Any change should be submitted as per ICH Q5E

Annexure 2

❖ **Registration process flow for Indigenous or locally developed Biosimilar products:**

1. Application for Research License

- ✓ Receiving Application for research license through Bengal Drug Rules 1946 Form-17
- ✓ Screening and evaluation
- ✓ Research license approval letter after satisfactory report.

2. Issuance of NOC for importation of any substances and cells etc. to manufacture biosimilar products:

- ✓ Receive application for NOC to import any substances and cells etc. to manufacture biosimilar products
- ✓ Screening and evaluation
- ✓ If become agreed Head of MA will send the file with NOC to DG, DGDA for approval.
- ✓ Receiving NOC after satisfactory report.

3. Approval to perform Preclinical Study:

- ✓ Receive application to perform Preclinical Study
- ✓ If Preclinical trials be conducted in overseas, apply to DGDA for NOC to send sample
- ✓ If Preclinical trials be conducted in Bangladesh, apply to DGDA for the approval of performing Preclinical study
- ✓ Head of MA will convey responsibility to CT function regarding document checking and evaluation related actions and after being satisfied will convene a meeting with pre- clinical advisory committee
- ✓ Preclinical advisory committee will give recommendations about submitted protocols.
- ✓ If satisfactory applicant will receive approval letter

4. Approval to perform Clinical trials:

- ✓ Receive application to perform Clinical Study
- ✓ If Clinical trials be conducted in overseas, apply to DGDA for NOC to send sample
- ✓ If Clinical trials be conducted in Bangladesh, apply to DGDA for the approval of performing Clinical study
- ✓ Head of MA will convey responsibility to CT function regarding document checking

and evaluation related actions and after being satisfied will convene a meeting with Clinical advisory committee

- ✓ Clinical advisory committee will give recommendations about submitted protocols.
- ✓ If satisfactory applicant will receive approval letter

5. Application for Registration of Biosimilar Products:

- ✓ Applicant will apply to DGDA for registration as per the Drug and Cosmetics Act, 2023 section 22 at front desk
- ✓ Applicant will apply with CTD Dossier format after getting source validation letter in both offline and online.
- ✓ CTD Dossier must be consists of 05 modules-
  - a) Module–1(Administrative and Prescribing Information)
  - b) Module–2(Quality Overall Summary)
  - c) Module–3 (Quality)
  - d) Module–4(Preclinical Study Report)
  - e) Module–5(Clinical Study Report)
- ✓ Application and receiving product sample at NDCL.
- ✓ Applicant will propose a brand name and the proposed brand name will be checked by MA department at DGDA database and applicant will receive a brand name of the product.
- ✓ Screening, Evaluation of Dossier and Moderator's comment
- ✓ After satisfactory evaluation report from MA, CT, PV and Lab, Head of MA will forward the report to DG, DGDA for approval along with the file & registration approval letter.
- ✓ If Reports found satisfactory, DG, DGDA will sign the registration approval letter.
- ✓ Applicant will receive approval letter.

6. Application for Packaging Material (SmPC, PIL etc.) Approval

7. Application for Issuance of Price certificate

8. Application for Issuance of MA certificate

9. Post Marketing Documents need to submit at DGDA

✓ Submission of stability data of first 3 manufacturing scale batches into the long-term stability program

✓ Phase-iv observational study on reasonable number of subjects for 6 months to 1 year.

✓ Any change should be submitted as per ICH Q5E

Annexure 3

❖ **Registration process flow for Imported Biosimilar products:**

1. Application for Registration of Biosimilar Products:

- ✓ Application for Marketing Authorization to DGDA with CTD Dossier and COPP (one of 7 reference developed countries or EMA according to DCC and Drug policy) in both offline and online.
- ✓ CTD Dossier must be consists of 05 modules-
  - a) Module–1(Administrative and Prescribing Information)
  - b) Module–2(Quality Overall Summary)
  - c) Module–3 (Quality)
  - d) Module–4(Preclinical Study Report)
  - e) Module–5(Clinical Study Report)
- ✓ Screening and Evaluation of Dossier
- ✓ After satisfactory evaluation report Head of MA will forward the report to DG, DGDA for approval along with the file & registration approval letter.
- ✓ If Reports found satisfactory, DG, DGDA will sign the registration approval letter.
- ✓ Applicant will receive approval letter.

2. Application for Packaging Material (SmPC, PIL etc.) Approval

3. Application for Issuance of Price certificate

4. Application for Issuance of MA certificate

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* This guideline should be read in conjunction with other relevant guideline.