SADC MRH PROJECT

BIOSIMILAR MEDICINES: QUALITY, NON-CLINICAL AND CLINICAL REQUIREMENTS FINAL DRAFT

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FOREWORD

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of biosimilar medicines. It represents the Southern African Development Community's (SADC) current thinking on the safety, quality and efficacy of medicines. It is not intended as an exclusive approach. Zazibona reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The Zazibona countries are committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants adhere to all the administrative requirements to avoid delays in the processing and evaluation of applications.

1 PREAMBLE

Biological medicines that are manufactured to be similar to registered reference medicines (unlike generic pharmaceutical medicines which are identical) are known as *biosimilars.* They are highly similar to the reference medicine in terms of structure, biological activity and efficacy, safety and immunogenicity profile.

The practices for registration of multisource "generic" pharmaceutical medicines do not apply to biological medicines. This guideline outlines the specific information required for registration of biosimilar medicines (see Scope). These types of biological medicines are similar to a reference product registered on the basis of a full complement of quality, safety and effectiveness data.

A full quality dossier (CTD) is required as detailed in current legislation and this should be supplemented by the demonstration of biosimilar comparability, as discussed in this guideline. Applicants should note that the comparability exercise for a biosimilar product versus the reference medicinal product is an additional element to the normal requirements of the quality dossier. It should be discussed separately in section 3.2.R when presenting the data in Module 3.

2 SCOPE

This guideline is applicable to biological medicines containing **well-characterized recombinant DNA-derived therapeutic proteins** that can be shown to be similar to a suitable reference biological medicine.
Vaccines, even if manufactured by recombinant DNA technology are excluded from the scope of this document.
Similar considerations should be applied if a synthetically produced follow-on protein references a biological medicine.
This guideline should be read in conjunction with all relevant current guidelines pertaining to medicinal products.

3 INTRODUCTION

The information requirements for a biosimilar application primarily include defined requirements for physico-chemical and biological comparability and reduced non-clinical and clinical evidence for safety and efficacy as outlined in this guideline.

The reference medicine is manufactured and controlled according to non-public proprietary methods that are not available to a "follow-on" developer; therefore, it is necessary that the applicant for a biosimilar medicine (who may use alternative protein expression systems and/or production technologies) provides evidence that the drug substance and final product are indeed similar in quality, safety and efficacy to the reference product.
If similarity cannot be demonstrated, the products cannot be considered to be biosimilar and full non-clinical and clinical data are required.

An appropriate comparability exercise is required to demonstrate that the biosimilar and the reference medicinal products have similar profiles in terms of physico-chemical properties, structure, biological activity, safety and efficacy (please refer to Annexure I, "Comparability Exercise").

This guideline outlines the quality, non-clinical and clinical requirements for biosimilar medicines.
The quality section addresses the physico-chemical, structural and functional requirements. The non-clinical section addresses the pharmaco-toxicological assessments. The clinical section addresses the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies, with assessment of the immunogenicity of the biosimilar medicines. The section on pharmacovigilance addresses the in-use safety of the medicine as well as the risk management plan.

Product class-specific annexures will supplement this guideline where a need is identified.
Where product class-specific guidelines are unavailable, Zazibona adopts European Medicines Agency (EMA) Committee for Medicinal Product for Human Use (CHMP) Guidelines.[7.1]

4 LEGAL BASIS

The guidance has been drafted to support the legal framework set out in the national legislation in member states. An alternative approach may therefore be used if such approach satisfies the requirements of the applicable statutes and regulations in the member states. The guidelines will apply in all SADC member states namely Angola, Botswana, Comoros, Democratic Republic of Congo, Eswatini, Lesotho, Madagascar, Malawi, Mauritius, Mozambique, Namibia, Seychelles, South Africa, Tanzania, Zambia and Zimbabwe. It is the marketing authorization holder's responsibility to ensure that the product information complies with all the relevant requirements for the application.

5 QUALITY, NON-CLINICAL AND CLINICAL DATA REQUIREMENTS

The demonstration of high similarity between the candidate biosimilar and the reference product is based on an extensive head-to-head comparability exercise consisting of comparative state-of-the-art physico-chemical, structural and in vitro functional tests, as well as non-clinical and clinical studies.

5.1 Quality and non-clinical data

The objective of the quality assessment is to establish the physicochemical properties of the biosimilar, and to show that it has no meaningful differences when compared to the reference medicine. Consideration should be given to the use of state-of the art analytical techniques.
A lack of detectable, meaningful differences between the biosimilar and the reference medicine may be the basis for reducing non-clinical and clinical requirements for registration of the biosimilar.
The relevance of observed differences in the physicochemical characteristics is explored using appropriate functional bio-assays, animal and clinical studies. Animal studies are seldom required in the development of biosimilars due to lack of sensitivity and/or availability of relevant animal models. (For further information, see section 5.1.3, "Non-clinical animal studies").

Validated assays that show the comparable functionality of the biosimilar and the reference in appropriate *in vitro* and sometimes, *in vivo*systems should be used. The functions that are selected for analysis should be shown to relate to the biological activity of the drug substance. All functions should be compared to the reference product activity and should be equivalent in those that are thought to be (major or minor) mechanisms of action, and no new activity is demonstrated that is not evident in the reference product.

Non-clinical studies should be performed before initiating clinical development, and should be comparative in nature, designed to detect differences in response between the biosimilar and the reference medicine and not just the response *per se*.

The design of an appropriate non-clinical study program requires a clear understanding of the product characteristics. Results from the physicochemical and biological characterisation studies should be reviewed to assess the potential impact on efficacy and safety. A holistic approach is necessary to include all available information in the development of the non-clinical and clinical studies leading to a successful application for registration.

Ongoing consideration should be given to the use of emerging validated technologies.
The approach taken to establish the chemical and molecular nature of the biosimilar drug substance, and to show that it has no detectable, relevant differences in physicochemical characteristics, when compared to the drug substance in the reference product, must be fully justified in the CTD non-clinical overview and/or the Quality Overall Summary.

Comparisons based on publications or pharmacopoeia monographs are not sufficient to establish similarities.

5.1.1 Quality Aspects

The applicant should provide a full quality dossier detailing the source–materials and excipients, manufacture, stability and control of the process in accordance with current Good Manufacturing Practices and other relevant guidelines[7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8]

The quality target product profile (QTPP) of a biosimilar should be based on data collected on the chosen reference drug product, including publicly available information and data obtained from extensive characterisation of the reference drug product. The QTPP should form the basis for the development of the biosimilar product and its manufacturing process.

The applicant should carry out a comprehensive physicochemical and biological characterisation of their drug product. Each of these analyses must be conducted in a head-to-head comparison with the reference drug product.

Molecular characterization should be as extensive as possible within limits of current technology – these studies should be conducted in head-to-head comparison with the reference product. Primary, secondary and tertiary structure should be demonstrated as well as the composition and structure of post-translational modifications and additions – e.g. glycosylation. Techniques used should include a search for, analysis and comparison of antigenic epitopes that could lead to adverse reactions.

Examples of tests that may be used for physicochemical characterization:

- Amino-acid sequence analysis of the purified product
- Peptide mapping
- Quantification of the drug substance by biological assays
- Molecular size analysis
- Characterization of higher order structure/s
- Identification of iso-forms
- Identification of post-translation modifications
- Quantification of truncated (extended) amino acid sequence impurities

Other factors to consider:

Chemical modification (e.g. oxidation, deamidation, methylation)
Aggregate formation
Impurities (e.g. presence of host cell proteins)
Glycosylation pattern

Structural differences which may be relevant to immunogenicity or allergenicity

The above list is by no means exhaustive.
To evaluate similarity, all aspects of product quality and heterogeneity should be assessed. Differences may be due to differences in source materials, process, impurities or excipients, and should be assessed for their relevance and potential impact on clinical safety and efficacy of the biosimilar and a justification (e.g. own-study results or literature data) of the actions taken to assess the relevance of such differences must be provided.

Differences in critical product quality attributes (i.e. those that are known to have potential impact on clinical activity) will add to the clinical testing required for the product. For example, if differences are found in glycosylation patterns that alter the biodistribution of the product and thereby change the dosing scheme, additional clinical testing for the product would likely be required. Differences of unknown clinical relevance, particularly regarding safety, may have to be addressed in additional pre- or post-marketing studies. [7.8]

Other differences between the biosimilar and reference substance may be acceptable, and would not trigger the need for extra clinical evaluation. For example, a therapeutic protein that has lower levels of protein aggregates could be thought to have a better safety profile than the reference and may not need added clinical evaluation.

5.1.2 Non-clinical in vitro studies

Comparative *in vitro* biological studies should be performed before initiating clinical development, and should be comparative in nature, designed to detect differences in response between the biosimilar and the reference medicine and not just the response *per se*.[7.2]

Bioassays that show the comparable functionality of the biosimilar and the reference medicine in appropriate *in vitro* systems should be used. The biological endpoints that are selected should be shown to relate to the clinical activity of the molecule. Design of an appropriate non-clinical study program requires a clear understanding of product characteristics. Results from the physiochemical and biological characterisation studies should be reviewed to assess the potential impact on biological activity, efficacy and safety.

The comparative in vitro studies include:

- receptor-binding studies (binding to, for example, receptors, antigens, enzymes) and/or
- cell-based assays (assays involving signal transduction and/or functional activity/viability of cells).

Both types of in vitro assays are expected to employ systems that are of known relevance for the pharmaco-toxicological effects of the reference product. These data which may already be available from quality-related bioassays, should normally be undertaken in order to establish comparability in functional activity and the likely causative factor(s) if comparability cannot be established. It should also be discussed to what degree the in vitro assays used are representative and/or predictive for the clinical situation according to current scientific knowledge.

5.1.3 Non-clinical animal studies

Where appropriate, comprehensive in vitro bioassays have shown product similarity and no potentially clinically significant quality differences (structure-wise or formulation-wise) have been observed, animal studies are generally not necessary.
In vivo animal studies to show comparable toxicology and activity, therefore, may only be required in some instances, for example, where there are uncertainties about the safety of a biosimilar product after extensive structural and functional characterization.

Animal studies should be designed to maximise the information obtained and to compare the biosimilar and reference medicine intended to be used in the clinical trials. Such studies should be designed to detect differences in response between the biosimilar and reference medicine and should be conducted in a species known to be relevant and sensitive, using appropriate, up-to-date, validated methods.

Where the model allows, consideration should be given to monitoring a number of endpoints such as:

a) Pharmacodynamic effect/activity relevant to the clinical application. These data should usually be available from biological assays in the pharmaceutical modules of the dossier.
b) Toxicity, including toxicokinetic measures in a relevant species
   Toxicokinetic measurements should include but not be limited to analysis of immunogenicity;
   - Determination of relevant antibody titres,
   - Where warranted due to biosimilar homology to endogenous proteins, analysis of anti-biosimilar antibody cross reactivity to endogenous proteins may be needed,
   - Depending upon PK assay format and PD markers, the characterization of neutralizing antibodies may be needed to interpret the study.
   - It may be relevant to analyse other forms of immune response.

The duration of the studies should be sufficiently long to allow detection of significant differences in toxicity and/or immune responses between the biosimilar and reference medicine.
If there are specific safety concerns, these might be addressed by including relevant observations (i.e. local tolerance) in the same repeat dose toxicity study.

Normally other routine toxicological studies such as safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not required for biosimilar medicines, unless indicated from results of repeat dose studies or other information[7.9].

Animal immunogenicity studies may be of value in demonstrating similarity of immune responses to reference and biosimilar products, but cannot be an alternative to immunogenicity studies in humans.

5.2 Clinical data

The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) studies followed by clinical efficacy and safety trial(s) or, in certain cases, PK/ PD studies may be sufficient for demonstrating clinical comparability [7.10]. All clinical studies should include assessment of immunogenicity of the biosimilar in comparison to the reference product (see section 5.2.5 “Immunogenicity”).

Clinical studies should have the following characteristics:

- The biosimilar is compared to the reference medicine (innovator). The biosimilar lot(s) used should be derived from the commercial manufacturing process and therefore, representing the quality profile of the lots to be commercialised.
- In general, an equivalence design should be used for clinical studies. The biosimilar should be equivalent to the reference product with respect to efficacy.

The study design requirements depend on the existing knowledge about the reference medicine and the claimed therapeutic indication(s). Available product-/disease-specific guidelines should be followed.

It is acknowledged that the manufacturing process will be optimised during development and before registration application. The required clinical data for the phase 3 comparability study should be obtained with the biosimilar product as produced with the final manufacturing process, formulation and specifications; and therefore representing the quality profile of the intended commercial batches. Any deviation from this should be justified and supported by adequate additional data.

For all clinical comparability trial designs, assay sensitivity has to be ensured[7.11]. Evidence must be presented to show that the end-point tests used have been validated and conducted by a competent and accredited laboratory.

5.2.1 Pharmacokinetic (PK) studies

Comparative PK studies designed to investigate key PK parameters (typically AUC, Cmax) are an essential part of demonstrating similarity. Specific considerations related to the inherent characteristics of proteins should be taken into account. [7.10] Differences in elimination characteristics between products e.g. clearance and elimination half-life may also be explored.

The choice of the design for single dose studies, steady-state studies, or repeated determination of PK parameters should be justified by the applicant. The crossover design is usually not appropriate for therapeutic proteins with a long half-life, e.g. therapeutic antibodies and pegylated proteins, or for proteins for which formation of specific antibodies is likely; parallel group designs should be considered.

To establish PK and/or PD similarity, the calculated confidence interval should fall within an acceptable limit. Selection of the confidence interval and the acceptable limits can vary among products. An appropriate starting point for an acceptable limit for the confidence interval of the ratio is 80–125%; if other limits are proposed, the sponsor should justify the limits selected for the proposed biosimilar product.

5.2.2 Pharmacodynamic (PD) studies

The pharmacodynamic (PD) markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product. The pharmacodynamic effect of the biosimilar and the reference medicine should be compared in a population where the possible differences can best be observed.
The design and duration of the studies must be justified. Combined PK/PD studies may provide useful information on the relationship between exposure and effect.
The selected dose should be in the steep part of the dose-response curve. The most appropriate dose level needs to be chosen.

5.2.3 Confirmatory pharmacokinetic/pharmacodynamic (PK/PD) studies

For biosimilar medicines, it is usual that comparative clinical trials of efficacy are required for the demonstration of clinical comparability. In certain cases, however comparative PK/PD studies between the biosimilar and the reference medicine may be sufficient to demonstrate clinical comparability, provided that all the following conditions are met:

a) The PK of the reference medicinal product is well characterised.
b) There is sufficient knowledge of the pharmacodynamic properties of the reference medicine, including the binding to its target receptor(s) and intrinsic activity. Sometimes, the mechanism of action of the biological product will be disease-specific.
c) The relationship between dose/exposure and response/efficacy of the reference medicine (the therapeutic "concentration-response" curve) is sufficiently characterised.
d) At least one PD marker is accepted as a surrogate marker for efficacy, and the relationship between dose/exposure to the product and this surrogate marker is validated and well known. A PD marker may be considered a surrogate marker for efficacy if therapy-induced changes of that marker can explain changes in clinical outcome.

Examples include absolute neutrophil count to assess the effect of granulocyte-colony stimulating factor, and early viral load reduction in chronic hepatitis C to assess the effect of alpha interferons. The choice of the surrogate marker for use in PK/PD studies should be justified.

If PK/PD studies are used to demonstrate comparability of the biosimilar, care should be taken to investigate a relevant dose range to demonstrate assay sensitivity.[7.10, 7.11]
The margins (limits) defining clinical comparability of PK and PD parameters must be defined *a priori* and justified.[7.11]

5.2.4 Clinical efficacy studies

The physicochemical, and non-clinical studies should be sufficient to establish molecular and functional similarity between the biosimilar and reference drug substances prior to any clinical studies of efficacy. Comparative clinical trials will be necessary to demonstrate clinical comparability between the biosimilar and the reference medicine, and not the clinical efficacy *de novo*. Clinical comparability margins should be pre-specified and justified, primarily on clinical grounds. As for all clinical comparability trial designs, assay sensitivity has to be ensured.

In general, an equivalence design should be used. The use of a non-inferiority design may be acceptable if justified on the basis of a strong scientific rationale and taking into consideration the characteristics of the reference product, e.g. safety profile/tolerability, dose range, dose-response relationship. A non-inferiority trial may only be accepted where the possibility of significant and clinically relevant increase in efficacy can be excluded on scientific and mechanistic grounds. However, as in equivalence trials, assay sensitivity has to be considered.[7.12, 7.13]

Where similarity in efficacy and safety have been demonstrated in a clinical trial for a particular indication, it may be possible to extrapolate efficacy to other indications of the reference product that have not been independently and specifically studied for the biosimilar medicine in clinical trials. In order to make this extrapolation, due consideration must be given to the following pharmacological/clinical aspects:

- The mechanism(s) of action in the indication of the reference product
- Differences, if any, in the expected PK and biodistribution of the product in different patient populations
- Differences, if any, in the expected immunogenicity risk of the product in different patient populations
- Differences, if any, in expected toxicities in each condition of use and patient population (including whether the expected toxicities are related to the pharmacological activity of the product or to off-target activities)
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which the reference product is licensed

Although, a non-inferiority design may be accepted for the main trial, demonstration of non-inferiority does not provide a strong rationale for the possibility of extrapolation to other indications of the reference drug product.
The safety and immunogenicity of the biosimilar product must also be sufficiently demonstrated or justified.

5.2.5 Immunogenicity

All clinical studies should include assessment of immunogenicity of the biosimilar in comparison to the reference product.[7.14]

An immune response to a therapeutic protein is usually detected by measuring ADAs. An ADA response may be transient and may not have any clinical consequences. However, ADAs may neutralize the effect of a biotherapeutic product and lead to a loss of efficacy. Safety problems may arise if the ADA response continues to evolve by immunoglobulin (Ig) class switch, antibody affinity maturation and epitope spreading. Life-threatening hypersensitive reactions may occur if the ADAs undergo a class switch to IgE or if pathogenic immune complexes (therapeutic protein + ADA) are formed. Another type of serious reaction is possible if the therapeutic protein has an endogenous counterpart. In this situation, ADAs may cross-react with the endogenous protein and cause serious complications, as noted in the case of anti-erythropoietin antibodies which cause pure red cell aplasia.

The assessment of immunogenicity requires a robust antibody testing strategy, characterisation of the observed immune response, as well as evaluation of the correlation between antibodies and pharmacokinetics or pharmacodynamics, relevant for clinical safety and efficacy in all aspects.

5.2.5.1 Immunogenicity Testing Principles

- Testing for immunogenicity should be performed by state of the art methods using assays with appropriate specificity and sensitivity. The screening assays should be validated and sensitive enough to detect low titre and low affinity antibodies. An assay for neutralising antibodies should be available for further characterisation of antibodies detected by the screening assays.
- The development of neutralizing antibodies and other types of specific immune response should be assessed in healthy individuals and in the different therapeutic indications.
- Immunogenicity data should be collected from a sufficient number of trial subjects to assess the development and variability of the immune response.
- The impact of these immune responses on the clearance/bioavailability of the biosimilar and on the continued safety and efficacy of the biosimilar in the different therapeutic indications should be assessed.
- Standard methods and international standards should be used whenever possible.
- The possible interference of the circulating antigen with the antibody assays should be taken into account.
- The periodicity, frequency and timing of sampling for testing of antibodies should be justified.
- In view of the unpredictability of the onset and incidence of immunogenicity, long term results of monitoring of antibodies at predetermined intervals will be required. In the case of chronic administration, one-year follow up data will be required prior to registration.
- The applicant should consider the possibility of antibodies to process related impurities.
- Consideration should be given to allergenicity of the product.

5.2.5.2 Evaluation of the clinical significance of the observed immune response

If a difference in the immune response to the biosimilar is observed as compared to the reference medicine, further analyses to characterise the antibodies and their implications to clinical safety, efficacy and pharmacokinetic parameters are required. Special consideration should be given to those products where there is a chance that the immune response could seriously affect the endogenous protein and its unique biological function.

The applicant should consider the role of immunogenicity in certain events, such as hypersensitivity, infusion reactions, autoimmunity and loss of efficacy. The applicant needs to propose activities to encourage the reporting of relevant adverse events, including events related to loss of efficacy.

5.2.6 Clinical safety

Even if the efficacy is shown to be comparable, the biosimilar may exhibit a difference in the safety profile (in terms of nature, severity, or frequency of adverse reactions). Pre-registration safety data

should be obtained in a number of patients sufficient to address the adverse effect profiles of the biosimilar and the reference medicine [7.154]. Care should be given to compare the type, severity and frequency of the adverse reactions between the biosimilar and the reference medicine.

5.3 Post-market requirements

Following registration of the biosimilar, the marketing authorization holder must comply with conditions of registration of the product.

5.3.1 Pharmacovigilance requirements

Data from pre-registration clinical studies are normally insufficient to identify all potential differences. Clinical safety (and efficacy) of the biosimilar medicine must, therefore, be monitored closely on an ongoing basis during the post-approval phase including continued benefit-risk assessment. Therefore, within the registration procedure the applicant should present a pharmacovigilance plan, as part of their risk management plan in Module 1[7.16] (See subsequent section 5.3.1, "Risk management plan"). Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

A key requirement for pharmacovigilance of biosimilars is the need to ensure continuous product and batch traceability in clinical use to support detection of any important safety issues that may be product- or batch-specific.

Biosimilars have the same International Nonproprietary Name (INN) as the reference product and must be readily distinguishable, preferably with an invented brand name. The use of the brand name will allow newly emerged and potential product-specific safety concerns to be rapidly identified and evaluated throughout the product lifecycle, and for the product to be traceable to location and patients. Accurate traceability of biosimilars by brand name and batch number must be assured in the post-marketing setting. The importance and method of traceability needs to be highlighted in the product information and on the product packaging or labelling as appropriate. For example, removable sticky labels on the product detailing brand name and batch number that can be recorded on patient records or 3D barcoding may be more appropriate for electronic records.
Where necessary, additional training to healthcare professionals should be provided to support reporting of brand name and batch number when reporting adverse reactions.

Following registration of the biosimilar, the marketing authorization holder must comply with conditions of registration. Their pharmacovigilance obligations will be closely monitored and reports of these activities, with defined timelines may be required. As per the national medicines regulatory authority's requirements, the routine Periodic Safety Update Reports[7.17] should also include information on adverse reaction reports, immunogenicity and any other information on tolerability or lack of efficacy that is applicable to the registration conditions.

It will be required that safety update information applicable to the reference medicine (product class) will be applicable to the biosimilar. This safety information must be evaluated and assessed by the marketing authorization holder of the biosimilar in a scientific manner with regard to causality of adverse events or adverse drug reactions and related frequencies and should report to the respective National Regulatory Agency on the actions that will be taken to ensure the safety of patients.

5.3.2 Risk Management Plan

A suitable Risk Management Plan (RMP) should be in place (or planned) for the biosimilar medicine at the time of application for registration.[7.18] This should be fully described in the CTD dossier in Module 1. The aim of the RMP is to document the risk management system considered necessary to

identify, characterise and minimise the important risks of the biosimilar. The RMP, therefore, is expected to contain the following information:

- the identification or characterisation of the safety profile of the medicinal product, with emphasis on important identified and important potential risks and missing information, and also on which safety concerns need to be managed proactively or further studied (the 'safety specification'). The safety specification should take into account risks identified during the biosimilar's development and potential risks associated with the use of the reference product.
- the planning of pharmacovigilance activities to characterise and quantify clinically relevant risks and to identify new adverse reactions (the 'pharmacovigilance plan'). Pharmacovigilance reporting procedures as defined by the National Medicines Regulatory Agency's guidelines should be adhered to;
- the planning and implementation of risk minimisation measures, including the evaluation of the effectiveness of these activities (the 'risk minimisation plan').

It may be necessary to include black and special population groups in these RMP activities. This RMP will form part of the conditions of registration.

Following registration, any specific safety monitoring requirement, safety update or package insert amendment imposed on the reference medicine or product class should be applied, unless a waiver for such a requirement has been approved by the NMRA.

6 GLOSSARY OF TERMS AND ABBREVIATIONS

The definitions given below apply to the terms used in this guideline. They may have different meanings in other contexts.

Biological Medicine
All medicines that contain a living organism, or are derived from a living organism or biological processes are considered Biological Medicines. They include, but are not limited to the following:

I. Plasma-derived and animal products, e.g. clotting factors, immunosera, Antivenoms;
II. Vaccines;
III. Biotechnology-derived medicines (rDNA products) e.g. rHu-antihaemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietins, nucleic acids;
IV. Products developed for human gene therapy.

Biosimilar or Biosimilar medicine
This is synonymous with *follow-on biologics* and *similar biotherapeutic products* (SBP). A biosimilar is a biological medicine that is highly similar to, but not necessarily identical, in terms of quality, safety and efficacy to an already registered reference biological medicine.

CTD
Common Technical Document, the format used for dossiers for application for registration of a medicine

DNA
Deoxyribonucleic acid

EMA
European Medicines Agency (Formerly EMEA)

Equivalence trial
An equivalence clinical trial is conducted to demonstrate that there is no clinically significant difference between a standard and an experimental treatment. The specified differences between the efficacies of the two treatments are shown to be no more than some pre-specified margin

Excipient
Any material added during formulation that does not have any pharmaceutical activity.

GMP
Good Manufacturing Practices.

Immunogenicity
The ability of a substance to trigger an immune response or reaction (*e.g*., development of specific antibodies, T cell response, allergic or anaphylactic reaction) following administration to an animal or human.

Non-inferiority trial
Not inferior to a comparator in the parameter studied. A non-inferiority clinical trial is one which has the primary objective of showing that the response to the investigational product is not clinically inferior to a comparator by a pre-specified margin[7.11].

Originator medicine

This is the innovator product - A medicine which has been licensed by a national regulatory authority which Authority aligns itself with on the basis of a full registration dossier; i.e. the approved indication(s) for use were granted on the basis of full quality, efficacy and safety data.

PD
Pharmacodynamic – the biochemical and physiological effects of drugs on the body and the mechanisms of drug action and the relationship between drug concentration and effect.

PK
Pharmacokinetic – the study of the mechanisms of absorption and distribution of an administered drug, the rate at which a drug action begins and the duration of the effect, the chemical changes of the substance in the body and the effects and routes of excretion of the metabolites of the drug.

Reference medicine
The comparator product used for head-to-head comparability studies with the biosimilar product in order to show similarity in terms of quality, safety and efficacy. It is a medicinal product registered on the basis of a full complement of quality, safety and effectiveness data.
The reference product must be sourced from a country that is regulated by a stringent regulatory agency (SRA). It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

Similar
This is the absence of a relevant (or significant) difference in the parameter of interest.

Stringent Regulatory Agency
A regulatory authority which is:

a) a member of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (as specified on www.ich.org); or
b) an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss medic and Health Canada (as may be updated from time to time);
c) or a regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time).

7 REFERENCES

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7.2 EMA: Guideline on Similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005)

7.3 EMA: Guideline on similar biological products (CHMP/437/04), the 'overarching guideline'

7.4 EMA: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: EMEA/CHMP/BMWP/42832/2005.

7.5 ICH Q8 Pharmaceutical development

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7.7 PIC/S. Guide to good manufacturing practice for medicinal products. Part 1. 2018

7.8 ICH Q9 Quality risk management

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7.14 WHO Questions and Answers: similar biotherapeutic products Complementary document to the WHO Guidelines on evaluation of similar biotherapeutic products (SBPs). WHO 2018

7.15 EMA: Guideline risk management systems for medicinal products for human use.

7.16 ICH E2E: Note for Guidance on Planning Pharmacovigilance Activities

7.17 ICH E2C (R1): Periodic Safety Update Reports

7.18 EMA: Guidance on the format of the risk management plan (RMP) in the EU – in integrated format. EMA/164014/2018 Rev.2.0.1 accompanying GVP Module V Rev.2

7.19 US FDA: Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations Guidance for Industry DRAFT GUIDANCE. 2019.

ANNEXURE I

Comparability Exercise

Introduction

The goal of the comparability exercise is to ascertain if the candidate biosimilar and the reference product are similar in terms of quality, safety and efficacy. Comparability exercise to demonstrate similarity should involve all aspects of development including full analytical comparability data on quality, and relevant studies for the non-clinical and clinical components. Comparative physicochemical and functional characterization studies should be sufficient to establish relevant quality attributes including those that define a product's identity, quantity, purity, potency and consistency.

It is not expected that the quality attributes in the candidate biosimilar and the reference product will be identical. For example, minor structural differences in the drug substance such as variability in posttranslational modifications may be acceptable, however they should be justified.

The extent of the studies necessary to demonstrate similarity will depend, amongst others, on the following:

- The nature of the product.
- The availability of suitable analytical techniques to detect potential product differences.
- The relationship between quality attributes and safety and efficacy
- Differences between the expression systems used to manufacture the biosimilar and the reference biologic drug.
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When assessing the similarity of the products, the manufacturer should also evaluate stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the drug product and, hence, potential differences in product-related substances and process-related impurities.

Quantitative ranges should be established for the biosimilar comparability exercise, where possible. These ranges should be based primarily on the measured quality attribute ranges of the reference drug product and should not be wider than the range of variability of the representative reference drug product batches, unless otherwise justified. The relevance of the ranges should be discussed, taking into account the number of reference drug product batches tested, the quality attribute investigated, the age of the batches at the time of testing and the test method used. A descriptive statistical approach to establish ranges for quality attributes could be used, if appropriately justified. It should be noted that acceptable ranges used for the biosimilar comparability exercise versus the reference drug product should be handled separately from release specifications.

Although the comparison of two independent products is outside of the scope of ICH Q5E: Comparability of Biotechnology/Biological Products Subject to Changes in their Manufacturing Process, some of the principles and approaches may be applicable.

Reference Product Considerations

Comparability with the reference product should address both the drug substance and drug product characteristics. The same reference product should be used throughout the comparability program and evidence of purchase of the reference product should be provided. Quality differences may impact the amount of non-clinical and clinical data needed.

Considering the inherent heterogeneity present in protein products and the expected batch-to-batch variability stemming from manufacturing processes, it is recommended that at least 10 reference product batches (acquired over a time frame that spans the shelf life of the reference product)[7.19], be included in the analytical assessment to ensure that the variability of the reference product is captured adequately. The final number of batches should be sufficient to provide adequate information regarding the variability of the reference product.

If the reference drug substance used for characterisation is isolated from a formulated reference drug product, additional studies should be carried out to demonstrate that the isolation process does not affect the important attributes of the drug substance.

Candidate Biosimilar Considerations

For the comparative analytical assessment, it is recommended that at least 6 to 10 batches of the proposed biosimilar be included to ensure:

1. adequate characterization of the proposed biosimilar and understanding of manufacturing variability.
2. adequate comparison to the reference product.

These batches should be representative of the intended commercial manufacturing process.

To the extent possible, the proposed biosimilar batches included in the comparative analytical assessment should be derived from different drug substance batches to adequately represent the variability of attributes inherent to the drug substance manufacturing process.

8 UPDATE HISTORY

Date	Reason for update	Version & publication
13/09/2019	First publication released for comment to agencies	Version 1
23/01/2020	Inclusion of comparability exercise annex	Version 2
	Editorial changes	
11/02/2020	Revision to improve clarity of text.	Version 3
03/11/2021	Editorial changes	Version 4
	Incorporation of revisions based on some comments from Industry	