TFDA/DMC/MRE/G/008

TANZANIA FOOD AND DRUGS AUTHORITY

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR MARKETING AUTHORIZATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS

(Made under Regulation 4 (1) of the Tanzania Food, Drugs and Cosmetics (Registration of Medicinal Products) Regulations, 2015

First Edition
January, 2019

P. O. Box 77150, EPI Mabibo, Off Mandela Road, Dar es Salaam, Tanzania
Tel: +255-22-2450512/2450751/ 2452108; Fax: +255-22-2450793
Email: info@tfda.or.tz; Website: **www.tfda.go.tz**

Table of Contents

Abbreviations and Acronyms ..... *iv*

Acknowledgments ..... *v*

Foreword ..... *vi*

Glossary of Terms ..... *vii*

1.0 Introduction ..... *xi*

1.1 The concept of similar biotherapeutic products xi

1.2 Scope xii

2.0 General Information *1*

2.1 General requirements 1

2.2 Consideration for the Choice of Reference Biopharmaceutical Products (SBP) 1

2.3 Product specific requirements 2

2.4 Other requirements 2

2.4.1 Manufacturer's declaration 2

2.4.2 Expert Report 3

2.4.3 Scientific guidance applicable to all similar biotherapeutic product 3

3.0 MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION *4*

4.0 MODULE 2: OVERVIEW AND SUMMARIES *4*

5.0 MODULE 3: QUALITY *4*

5.1 Qualitative and Quantitative Particulars 5

5.2 Manufacturing process 5

5.3 Analytical Comparability studies 6

5.4 Analytical procedure/technique/Product characterization 7

5.5 Container closure system 8

5.6 Product stability 8

6.0 MODULE 4: NON CLINICAL STUDY 9

6.1 Special consideration 9

6.2 Quality-related factors 10

6.3 Pharmacodynamics 10

6.4 Toxicology 11

7.0 MODULE 5: CLINICAL STUDY 12

7.1 Pharmacokinetic (PK) studies 12

7.2 Pharmacodynamics (PD) studies 13

7.3 Clinical efficacy trials 13

7.4 Clinical safety and effectiveness 14

7.5 Clinical Immunogenicity 15

7.6 Pharmacovigilance 16

APPENDIX 1: APPLICATION FORM FOR MARKETING AUTHORIZATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs) 18

1.16.1 20

1.16.2 20

Name(s) and physical address(es) of the manufacturer(s) of the drug substance 20

APPENDIX 2: PUBLIC ASSESSMENT SUMMARY INFORMATION FOR SIMILAR BIOTHERAPEUTIC PRODUCT 24

References: 36

Abbreviations and Acronyms

BMRs	-	Batch Manufacturing Records
CMC	-	Chemistry, Manufacturing and Controls
CA	-	Clinical Assessor
DNA	-	Deoxyribonucleic Acid
EAC	-	East African Community
EMA	-	European Medicines Agency
EU	-	European Union
GCP	-	Good Clinical Practice
GLP	-	Good Laboratory Practice
GMP	-	Good Manufacturing Practice
ICH	-	International Council for Harmonization
INN	-	International Non-proprietary Names
MOA	-	Mechanism of Action
NCE	-	New Chemical Entity
NMRA	-	National Medicines Regulatory Authority
Ph. Eur	-	European Pharmacopeia
PK/PD	-	Pharmacokinetic/Pharmacodynamic
PBRER	-	Periodic Benefit-Risk Evaluation Report
RBP	-	Reference Biotherapeutic Product
RMP	-	Risk Management Plan
SBP	-	Similar Biotherapeutic Product
SRAs	-	Stringent Regulatory Authorities
TFDA	-	Tanzania Food and Drugs Authority
WHO	-	World Health Organization

Acknowledgments

Development of these guidelines was undertaken in order to address the challenges faced by our Applicants who wish to apply for marketing authorization of similar biotherapeutics products.

This work would not have been possible without EAC Partner States' NMRAs, Regional and International Organizations and EAC Secretariat and members of the Expert Working Group (EWG) on Medicines Evaluation and Registration (MER) of the East African Community Medicines Regulatory Harmonization (EAC MRH) Programme who actively participated in the development of the guidelines.

I am especially indebted to TFDA staff who worked actively from the initial stages of drafting the guidelines. Further, I am grateful to esteemed stakeholders; the dealers in pharmaceutical industry and the academia in particular members of the Tanzania Pharmaceutical Manufacturers Association (TPMA) and the Tanzania Association of Pharmaceutical Industries (TAPI) who discussed the draft guidelines and gave commendable inputs for improvement.

Lastly, I wish to thank the African Medicines Regulatory Harmonization (AMRH) program partners, namely World Health Organization (WHO), International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) for their valuable inputs and all individuals and institutions who have supported the development of these guidelines.

Akida M. Khea
Acting Director, Medical Products Control
Tanzania Food and Drugs Authority

Foreword

The Tanzania Food and Drugs Authority Act, Cap 219, requires that all medicinal products intended to be marketed in the country must meet the acceptable standards of quality, safety and efficacy and at the same time be assessed to have been produced in facilities that comply with current Good Manufacturing Practices (GMP).

The guidelines apply to well-established and well-characterized biotherapeutic products such as recombinant DNA-derived therapeutic proteins. Vaccines and plasma derived products and their recombinant analogues are excluded from the scope of these guidelines.

These guidelines are therefore made to provide guidance to applicants on the procedure for registering a Similar Biotherapeutic Product in Tanzania. It provides guidance on issues to consider when demonstrating that a proposed biotherapeutic product is similar to a reference biotherapeutic product which is already registered and well established.

Submission of satisfactory comparability data on the quality, safety, and efficacy of the Similar Biotherapeutic Product to the Reference Biotherapeutic Product will enable the Authority to assess the suitability of the product for its intended use in the country. If a product is registered in the country, the Authority will continue to monitor the products once they are on the market. The Authority will also assess the suitability of Similar Biotherapeutic Products for export from country. Applicants are therefore encouraged to acquaint themselves with this document before completing the registration form.

These guidelines should be read in conjunction with Guideline for the Registration of Biotherapeutic products.

Adam M. Fimbo
Acting Director General
Tanzania Food and Drugs Authority

Glossary of Terms

In these guidelines, unless the context otherwise states: -

"Antibody" means a spectrum of proteins of the immunoglobulin family that is produced, in the human (or animal) body, in response to an antigen (e.g., a virus or bacterium, or a foreign protein unknown to the body's immune system). Antibodies are able to combine with and neutralize the antigen, as well as to stimulate the immune system for defense reactions.

"Antigen" means a substance that causes the immune system to produce antibodies against it.

"Drug substance "means an antigenic substance (or compounds thereof) that can induce specific responses in human against infectious agents, its antigens and toxins.

"**Applicant"** means the product owner or license holder. Representatives of license holders may not hold themselves as applicants unless they own the product.

"Batch/Lot" means a defined quantity of starting material, packaging material or product processed in one process or series of processes so that it can be expected to be homogenous.

"Bioequivalence" means that two proprietary preparations of a drug, when administered in the same dose and by the same route, will have the same bioavailability, duration of action and efficacy.

"Biotechnology" means a set of tools that employ living organism (or part of organism) to make or modify products, to improve plants and animals, or to develop microorganisms for specific uses Or a collection of technologies that use living cells and/or biotherapeutic product molecules to solve problems or make useful products.

"Chemically synthesized polypeptide" means any alpha amino acid polymer that is (a) made entirely by chemical synthesis, and (b) is less than 100 amino acids in size.

"CMC (Chemistry, Manufacturing and Controls)" means the section of a submission dealing with the substance properties, manufacturing and quality control, intended for evaluating the provided information in the context of the current standards in chemical science and technology, and the current regulations.

"Comparability Exercise" means the activities including study design, conduct of studies, and evaluation of data, that are designed to investigate whether the products are comparable (head to head comparison).

“Conformance to specification” means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria.

“biotherapeutic product”. A biotherapeutic product medicinal product with the indications of treating human diseases

“Equivalent” means equal or virtually identical in the parameter of interest. Small non-relevant differences may exist. Equivalent efficacy of two medicinal products means they have similar (no better or no worse) efficacy and any observed differences are of no clinical relevance.

“Genetic engineering” means the technique by which heritable material, which does not usually occur or will not occur naturally in the organism or cell concerned, generated outside the organism or the cell is inserted into said cell or organism. It shall also mean the formation of new combinations of genetic material by incorporation of a cell into a host cell, where they occur naturally (self-cloning) as well as modification of an organism or in a cell by deletion and removal of parts of the heritable material.

“Head-to-head comparison” means the direct comparison of the properties of the similar biologic with the reference biologic in the same study.

“Immunogenic” means any substance that is recognized as foreign by the immune system in a (particular) higher organism and induces an immune response which may include the formation of antibodies and developing immunity, hypersensitivity to the antigen, and tolerance.

“Immunogenicity” means 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).

“Impurity” means any component present in the drug substance or drug product that is not the desired product, a product-related substance, or excipients including buffer components. It may be either process- or product-related.

“Innovator Product” means a means a new chemical entity which has received a patent on its chemical formulation or manufacturing process, obtains chemical formulation or manufacturing process, obtains approval from a regulatory authority after extensive testing and is sold under a brand name.

“In-process control or Process control” means checks performed during production to monitor and, if appropriate, to adjust the process and/or to ensure that the intermediate or API conforms to its specifications.

Interchangeability” is the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative, or with the agreement of the prescriber. For interchangeable products, one or the other can be used (prescribed) but these products cannot be substituted with one another during a treatment period. Hence, interchangeability does not imply substitutability.

“International Non-proprietary Name (INN)” means the approved chemical name of the product.

“Non-clinical (Pre-clinical)” means during pre- clinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing.

“Pharmacopoeias” means a current edition of British Pharmacopoeia, (BP), European Pharmacopoeia, (Ph. Eur), International Pharmacopoeia, (Int. Ph), United States Pharmacopoeia, (USP), Japanese Pharmacopoeia (JP).

“Pharmacovigilance” means, the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems.

“Protein” means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acid in size.

“Reference Biotherapeutic Product”
A reference biotherapeutic product is used as the comparator for head-to-head comparability studies with the similar biotherapeutic product in order to show similarity in terms of quality, safety and efficacy. Only an originator product that was licensed on the basis of a full registration dossier can serve as a RBP.

“Similar Biotherapeutic Product” means a biotherapeutic product claimed to be similar‟ to an already approved reference biotherapeutic product, which is marketed by an independent applicant, subject to all applicable data protection periods and/or intellectual property rights in the innovator product.

“Similar” means absence of a relevant difference in the parameter of interest.

“Similarity” means if a company chooses to develop a biotherapeutic product claimed to be „similar“ to a reference product, comparative studies are needed to generate evidence substantiating the similar nature, in terms of quality, safety and efficacy, of the biotherapeutic product and the chosen reference product.

“Specification” means a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a drug substance, drug product or materials at other stages of its manufacture should conform to be considered acceptable for its intended use.

“Substitution” Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber.

“Switching” Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment.

“Validation” The process of demonstrating that the system (or process) under consideration meets in all respects the specification of that system or process. Also, the process of evaluating a system or component during or at the end of the development process to determine whether it satisfies specified requirements.

“Well-characterized biologic” A well-characterized biologic is an entity whose identity, purity, impurities, potency and quantity can be determined and controlled. Most of these products are recombinant DNA-derived proteins or monoclonal antibodies. For DNA-derived proteins, determining identity requires establishing the primary and secondary structures, including amino acid sequence, disulfide linkages (if possible), and post-translational modifications such as glycosylation (the attachment of carbohydrate side chains to the protein). Monoclonal antibodies can be identified with rigorous physicochemical and immunochemical assays. Purity and impurities must be quantifiable, with impurities being identified if possible; the biotherapeutic product activity and the quantity must be measurable.

Well-established biotherapeutic product: A biotherapeutic product that has been marketed for a suitable period of time with a proven quality, efficacy and safety.

1.0 Introduction

These guidelines were developed to describe the regulatory framework for SBPs in EAC countries, which align with current global regulation of SBPs. It is intended to guide applicants on the Chemistry, Manufacturing and Control (CMC) section of a marketing application for proposed similar biotherapeutic products. The marketing application must include information demonstrating bio similarity, based on data derived from, among other things, analytical studies that demonstrate that the biotherapeutic product is highly similar to the Reference Biotherapeutic Product notwithstanding minor differences in clinically inactive components.

Although the regulatory framework applies generally to biotherapeutic product products, this guidance document focuses on similar biotherapeutic products and provides an overview of the quality, non-clinical and clinical factors to consider in demonstrating biosimilarity between a proposed biotherapeutic product and the reference product.

SBPs can be approved based in part on an exercise to demonstrate similarity to an already approved RBP by Stringent Regulatory Authorities (SRAs). The same RBP should be used throughout the comparability program in order to generate coherent data and conclusions. Comparative quality, non-clinical and clinical studies are needed to substantiate the similarity of structure/composition, quality, safety and efficacy between the biosimilar and the reference biotherapeutic product. The pharmaceutical form, strength/concentration and route of administration should be the same as that of the reference product. Any differences between the similar biotherapeutic product and the reference biotherapeutic product should be justified by appropriate studies.

1.1 The concept of similar biotherapeutic products

The concept of a Similar Biotherapeutic Product (SBP) applies to biotherapeutic product drug submission in which the manufacture would be based on demonstrated similarity to a Reference Biotherapeutic Product (RBP).

The rationale for creating the new regulatory framework to evaluate SBP is based on claim to be highly similar to a reference biotherapeutic product. Similar biotherapeutic product does not usually meet all the conditions to be considered as a generic product. The term generic medicine is used for chemically derived products which are identical and therapeutically equivalent to the innovator product. For such generics, demonstration of bioequivalence with the innovator product is usually appropriate to infer therapeutic equivalence. However, this procedure cannot be used for SBP. The large and complex molecular structure of biotherapeutics makes them difficult to adequately characterize in the laboratory.

Based on the current analytical techniques, two biotherapeutic products produced by different manufacturing processes cannot be shown to be identical, but similar at best. For these reasons, the standard generic approach is scientifically not applicable to development of SBP products and additional non-clinical and clinical data are usually required.

Based on the comparability approach and when supported by state-of-the-art analytical systems, the comparability exercise at the quality level may allow a reduction of the non-clinical and clinical data requirements compared to a full dossier. This in turn, depends on the clinical experience with the substance class and will be a case by case approach.

The aim of the biosimilar approach is to demonstrate close similarity of the 'similar biotherapeutic product' in terms of quality, safety and efficacy to one chosen reference medicinal product, subsequently referring to the respective dossier.

1.2 Scope

This guideline applies to well-characterized and established molecules, their derivatives and products of which they are components, and which are isolated from microorganisms, tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the generation and submission of efficacy, Potency, stability and toxicological data for biotherapeutics products such as cytokines (interferons, interleukins, colony-stimulating factors, and tumour necrosis factors), erythropoietin, plasminogen activators, growth hormones and growth factors, insulins, and monoclonal antibodies.

The document does not cover Conventional drugs, allergenic extracts, vaccines, blood and blood products, heparins, and in-vitro diagnostic

2.0 General Information

2.1 General requirements

For general requirements of application for marketing authorization of SBPs, reference should be made to the Guidelines on Documentation for Marketing Authorization of Biotherapeutic Products, available at TFDA website.

These guidelines are composed of template (*Appendix 2*) of the Summary Information for Similar Biotherapeutic Product (SIB) of which general information of the product should be filled out by Marketing Authorization Holder (MAH). The SIB should be filled out and include in the product dossier submission. For any amendment introduced after approval, SIB should be updated accordingly.

SBP submission must follow the format described in Guidelines on Documentation for the Marketing Authorization of Biotherapeutic Products. Due to nature of SBP, some CTD sections described in Guidelines on Documentation for Marketing Authorization of Biotherapeutic Products may not be applicable. In this regard, precise guidance is provided in module 3, 4 and 5 of this document.

2.2 Consideration for the Choice of Reference Biopharmaceutical Products (SBP)

The aim of the SBP approach is to demonstrate close similarity of the SBP product in terms of quality, safety and efficacy to a RBP. The following should be considered in selecting RBP: -

(a) The RBP should have been marketed for a suitable duration and have a volume of marketed use such that the demonstration of similarity to it brings into relevance a substantial body of acceptable data regarding the safety and efficacy.
(b) The manufacturer must demonstrate that the chosen RBP is suitable to support the application for marketing authorization of SBP.
(c) The RBP should have been licensed on the basis of full quality, safety, and efficacy data. An SBP should therefore not be chosen as an RBP.
(d) The same RBP should be used throughout the development of the SBP (i.e. throughout the comparative quality, nonclinical, and clinical studies).
(e) The active ingredient of the RBP and the SBP must be shown to be similar.
(f) The dosage form and route of administration of the SBP should be the same as that of the RBP.
(g) The following factors should be considered in the choice of an RBP that is marketed in another jurisdiction:

(i) The RBP should be licensed and widely marketed in another jurisdiction that has a well-established regulatory framework and principles, as well as considerable experience of evaluation of biotherapeutic products and post-marketing surveillance activities.
(j) The acceptance of an RBP for evaluation of an SBP does not imply that the TFDA have approved the RBP for use.

2.3 Product specific requirements

It should be recognized that there may be subtle differences between SBPs from different manufacturers or compared with reference products, which may not be fully apparent until greater experience in their use have been established. Therefore, in order to support pharmacovigilance monitoring, the specific SBPs given to patient should be clearly labeled and identified (by the brand name) by the prescriber.

Application submitted for the registration of SBPs should contain, among other things, data demonstrating that the SBP is similar to a RBP which should be derived from:-

(a) Analytical assessment (physicochemical and functional studies) demonstrating the biotherapeutic product is highly similar to the reference product regardless of minor differences in clinically inactive components.
(b) Animal studies, including the assessment of toxicity.
(c) A clinical study or studies, including the assessment of immunogenicity and pharmacokinetics or pharmacodynamics, that are sufficient to demonstrate safety, purity, and potency in one or more appropriate indications of use for which the reference product is registered and intended to be used and for which registration is sought for the biotherapeutic product.
(d) Risk management/pharmacovigilance plans.

2.4 Other requirements

2.4.1 Manufacturer's declaration

A declaration document should be presented certifying that the information provided corresponds to all the studies performed, regardless of their results. This should include all the pertinent information regarding all toxicological and/or clinical tests or trials of the biotherapeutic product that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application.

2.4.2 Expert Report

Experts must provide summary reports of the documents and particulars, which constitute sections 3, 4 and 5.
The requirement for these signed Expert Reports may be met by providing: -

(a) The Quality Overall Summary, Non-clinical Overview/Summary and Clinical Overview/Summary.
(b) A declaration signed by the experts.
(c) Brief information on the educational background, training and occupational experience of the experts

Experts should additionally indicate in their declarations the extent, if any of their professional or other involvement with the applicant/dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom. Reports should be based on an independent assessment of the dossier and references must be provided for any additional claims not supported by the dossier.

2.4.3 Scientific guidance applicable to all similar biotherapeutic product

For product specific guidance's, applicants are encouraged to refer to the products specific guidelines available at the following reference websites:

(a) EMA: http://www.ema.europa.eu.
(b) International council of Harmonisation (**ICH**) Guidelines: http://www.ich.org.
(c) WHO TRS 977, Annex 2, i.e. WHO biosimilar guidelines.

Note:
The submission must follow CTD format detailed in Guidelines on Submission for Documentation for Registration of Biotherapeutics Products. The sections below provide specific requirements to Similar Biotherapeutic Products dossiers that are submitted for marketing authorization.

3.0 MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative information as stipulated in the Guidelines for the Marketing Authorization of Biotherapeutic products.

The Summary of Product Characteristics (SmPC) or Prescribing Information (PI) for the SBP should be as similar as possible to that of the RBP except for product-specific aspects, such as different excipient(s). This is particularly important for posology and safety-related information, including contraindications, warnings and adverse events. However, if there are fewer indications for the SBP than for the RBP, the related text in various sections may be omitted unless it is considered important to inform doctors and patients about certain risks, e.g. as a result of potential off-label use. In such cases it should be clearly stated in the prescribing information that the SBP is not intended for use in the specific indication(s) and the reasons why.

Labelling of biosimilars should be individualized. It should be clearly identifiable by a unique brand name. Where an INN is defined, this should also be stated.

The SmPC/PI and Labelling should follow the Guidelines on Format and Content of Summary of Product Characteristics for Pharmaceutical Products and Guidelines on Format and Content of Labels, available in the TFDA website.

4.0 MODULE 2: OVERVIEW AND SUMMARIES

The purpose of this module is to summarize the quality, nonclinical and clinical information presented in modules III, IV, and V in the market authorization application. The submission for this section will be as stipulated in the Guideline for the Marketing Authorization of Biotherapeutic products.

5.0 MODULE 3: QUALITY

The information requested under this section should be provided in the format stipulated in the Guideline for the Marketing Authorization of Biotherapeutic products.

The quality part of a SBP, like all other biotherapeutic product should comply with established scientific and regulatory standards. SBP manufacturer should provide full information on manufacturing process, characterization, specifications, analytical procedures and stability.

Manufacturer is required to submit extensive data focused on the similarity, including comprehensive comparative (head – to- head) physicochemical, molecular and biotherapeutic product characterization (these may include bioassays, biotherapeutic product assays, binding assays, and enzyme kinetics) of the SBP and the RBP.

Information on the development studies conducted to establish the dosage form, the formulation, manufacturing process, stability study and container closure system including integrity to prevent microbial contamination and usage instructions should be provided.

A summary of the analytical results (these may be in a form of a report) on three consecutive batches of finished product should be provided to demonstrate consistency in quality from batch to batch. These batches may be pilot or production batches. If they are pilot batches, they must be representative of production batches

5.1 Qualitative and Quantitative Particulars

Qualitative and Quantitative Particulars of SBP shall be presented in a tabular form as indicated in the Guideline for the Marketing Authorization of Biotherapeutic products. A list of all components/excipients of the SBP and diluents (if applicable) should be provided. Quantities per dose should be stated for all components. A clear description of the active ingredient including the name(s) of the active ingredient should be provided. The reason(s) for inclusion of each component and a justification for overages should also be stated.

Where applicable; special characteristics of excipients should be indicated. The type of water (e.g. purified, demineralised), where relevant, should be indicated.

5.2 Manufacturing process

The manufacturing process for SBP should be highly consistent and robust. The process should be developed and optimized taking into account state-of-the-art technology in relation to the manufacturing processes and consequences on product characteristics. For the establishment and characterization of the cell banks, refer Guidelines for the Marketing Authorization of Biotherapeutic products together with ICH guidelines: Q5A, Q5B and Q5D.

Complete description of the manufacturing process from the development and characterization of cell banks, stability of clone cell culture/fermentation, harvest, excipients, formulation, purification, primary packaging interactions should be submitted.

When demonstrating similarity between a SBP and a RBP, the following factors should be critically considered: -

(a) Differences between the chosen expression system of the proposed SBP and that of the RBP should be carefully considered and appropriately documented.

(b) Characterization of the expression construct, including its genetic stability, should be demonstrated in accordance with principles recommended in ICH Q5B.
(c) Characterization tests, process controls, and specifications that will emerge from information gained during process development must be specific for the proposed SBP and the manufacturing process. The use of Quality-by-Design approaches is recommended to assure consistent manufacturing of high-quality product.
(d) The manufacturing process validation protocol and report should be submitted.
(e) Product employing clearly different approaches to manufacture from the reference product will not be eligible for registration as a SBP. The applicant shall be required to provide information to fulfill the requirements for registration of new biotherapeutic product as prescribed in the Guideline for the Marketing Authorization of Biotherapeutic products.

Reference

i. ICH Q5A: Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guidele/2009/09/WC500002801.pdf)

ii. ICH Q5B: Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products. http://www.gmp-manual.com/showdoc/GMP-MANUAL/GMP-Regulations/E-ICH-Guidelines/E5B-ICH-Q5B-Quality-of-Biotechnological-Products-Analysis-of-the-Expression-Construct-in-Cells-Used-for-Production-of-R-DNA-Derived-Protein-Products.

iii. ICH Q5D: Derivation and Characterization of Cell Substrates used for Production of Biotechnological/Biotherapeutic product http://www.gmp-manual.com/showdoc/GMP-MANUAL/GMP-Regulations/E-ICH-Guidelines/E5D-ICH-Q5D-Derivation-and-Characterisation-of-Cell-Substrates-used-for-Production-of-BiotechnologicalBiotherapeutic product-Products.

5.3 Analytical Comparability studies

The SBP should be highly similar to the RBP and studies shall be done according to the capability of available appropriate analytical assays to assess, for example, the molecular weight of the protein, complexity of the protein (higher order structure and post-translational modification), degree of heterogeneity, functional properties, impurity profiles and degradation profile denoting stability. Design of the Comparability approach should be supported by scientifically sound methodologies.

Note:
The capabilities of the methods used in the analytical assessment as well as their limitations shall be described.

5.4 Analytical procedure/technique/Product characterization

The applicant should submit assessment of the analytical similarity to the RBP in additional to information on Chemistry, Manufacturing and Controls (CMC). The purpose of the analytical similarity assessment should be clearly described with consideration for the known quality attributes and performance characteristics of the specific reference product.

Extensive analytical methods should be applied to increase the likelihood of detecting subtle variations in the quality attributes of the product. Methods used in both the characterization studies and comparability studies should be appropriately qualified and validated.

Reference standards and international reference materials shall be used for method qualification and validation. Specifications and certificates of analysis for both reference standards and raw materials from the manufacturer should be provided.

Characterization of a biotherapeutic product by appropriate techniques, as described in ICH Q6B and WHO TRS 987 annex 4 should include the determination of physicochemical properties, biotherapeutic product activity, immunochemical properties, purity, impurities, contaminants, and quantity. Product-related impurities, product-related substances, and process-related impurities should be identified, characterized as appropriate, quantified and compared to those of the RBP to the extent feasible and relevant, as part of an assessment of the potential impact on the safety, and potency of the product.

For further guidance on key points to be considered in the characterization exercise, ICH Q6B guidelines shall be referred to.

Reference

i. ICH Q2: Validation of Analytical Procedure: Test and Methodology; http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

ii. ICH Q6B: Note for guidance on specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biotherapeutic product.

iii. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002824.pdf

5.5 Container closure system

A description of the container and closure system, and its compatibility with the SBP shall be submitted. Detailed information concerning the supplier(s), address (es), and the results of any relevant information on compatibility, toxicity and biotherapeutic product tests shall be provided for containers of novel origin. Evidence of container and closure integrity shall be provided for the duration of the proposed shelf life. Drawings of the containers and closures should be included.

Specifications shall be provided for the components of the container closure system that come into contact with the product. Specifications for primary container shall include among other tests, an identification test for material of construction of the container.

5.6 Product stability

The stability studies should comply with relevant EAC Guidelines for application of Registration for Biotherapeutics, ICH Q5C and Q1A (R2). Studies should be carried out to show that the biodegradation profiles are comparable between SBP and RBP. Generally, stability studies results should be summarized in a tabular format, and they should include the results from real time and accelerated degradation studies and studies under various stress conditions (temperature, light, humidity and mechanical agitation).

An appropriate physicochemical and functional comparison of the stability of the proposed SBP with that of the RBP should be monitored to confirm storage conditions selected.

Stability data should be provided for at least three representative consecutive batches stored in the final container. The three consecutive production runs shall (the largest scale validated and proposed for registration for commercial use). The storage temperature should be stated together with the results of tests on the batches. A plan for on-going stability studies should be provided indicating the batch numbers of the batches on test and the time points when testing is planned.

Note:
Shelf life before opening the container and shelf-life after first opening the container (if applicable) shall be demonstrated.

Reference:

i. ICH Q5C - Quality of Biotechnological Products: Stability Testing of Biotechnological/Biotherapeutic Products: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002803.pdf.

ii. Q1A (R2) - Stability Testing of New Drug Substances and Products**:** http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf.

6.0 MODULE 4: NON CLINICAL STUDY

The establishment of safety and efficacy of a SBP usually requires the generation of some non-clinical data with the SBP. The spectrum of studies required to established safety and efficacy of the SBP may vary considerably and should be defined on a case-by-case basis.

Non-clinical studies should be performed in a facility that is GLP accredited. Certificate of GLP compliance issued by competent authority should be included in the dossier.
These studies should be comparative in nature and should be designed to detect differences in the pharmaco-toxicological response between the SBP and the RBP.

The approach taken will need to be fully justified in the non-clinical overview. Nonclinical studies should be a part of the overall comparability studies. Any deviation from this approach should be appropriately justified.

6.1 Special consideration

The design of an appropriate nonclinical study should consider the product characteristics. Results from the physicochemical and biotherapeutic product characterization studies should be reviewed from the point of view of potential impact on efficacy and safety. In the development of SBP, existing guidelines such as EAC Guideline for the Marketing Authorization of Biotherapeutic products and ICH S6, should also be consulted.

Reference:

i. Guidance for Industry: S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074957.pdf

Additional nonclinical data may be required to establish the safety and efficacy of SBP depending on the product and on factors related to substance class as stipulated in the Guideline for Marketing Authorization of Biotherapeutic products.

Factors that may elicit the need for additional nonclinical studies include, but are not restricted to, the following:

6.2 Quality-related factors

i. Significant differences in the cell expression system compared with the RBP;
ii. Significant differences in purification methods used;
iii. The presence of a complex mixture of less well-characterized product- and/or process-related impurities e.g. a highly complex immunogenic substance that is difficult to characterize by analytical techniques and that possesses a narrow therapeutic index.

a) Factors related to pharmaco-toxicological properties of the drug substance:
i. Mechanism(s) of drug action are unknown or poorly understood;
ii. The drug substance is associated with significant toxicity and/or has a narrow therapeutic index;
iii. Limited clinical experience with the RBP.

Depending on these factors, the spectrum of studies required to establish the safety and efficacy of the SBP may vary considerably and should be defined on a case-by-case basis.

6.3 Pharmacodynamics

a) In vitro studies:
In order to assess any alterations in reactivity between the SBP and the RBP, data from a number of comparative bioassays (e.g. receptor-binding studies, cell proliferation assays), many of which may already be available from quality-related bioassays, should be provided.

b) In vivo studies:
Animal studies should be designed to maximize the information obtained. They should be comparative in nature (see above), should be performed in a species known to be relevant (i.e. a species in which the RBP has been shown to possess pharmacodynamic and/or toxicological activity), and should employ state-of the-art technology.

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

a) Biotherapeutic product/pharmacodynamic activity relevant to the clinical application. These data should usually be available from biotherapeutic product assays described in the quality part of the dossier (Section 3) and reference to these studies can be made in the nonclinical part of the dossier.

b) If feasible, biotherapeutic product activity may be evaluated as part of the nonclinical repeat-dose toxicity study (described below). Invivo evaluation of biotherapeutic product/pharmacodynamic activity may be unnecessary if in vitro assays are available that have been validated as reliably reflecting the clinically relevant pharmacodynamic activity of the RBP.At least one PD marker is accepted as surrogate marker but must be validated.

6.4 Toxicology

Data on at least repeated dose toxicity conducted in relevant specie should be submitted.

Toxicokinetic measurements shall include the following;

(a) Determination and characterization of antibody responses, including anti-product antibody titres

(b) Cross-reactivity with homologous endogenous proteins, and

(c) Product-neutralizing capacity.

The studies should be of sufficient duration to allow detection of potential differences in toxicity and antibody responses between the SBP and the RBP.

A head-to-head repeat dose toxicity study should usually constitute a minimum requirement for non-clinical evaluation of a SBP**.** Comparative repeat-dose toxicity studies should be submitted to demonstrate that no "unexpected" toxicity will occur during clinical use of the SBP. The repeat-dose toxicity study performed on the final formulation should aim at detecting potential toxicity associated both with the drug substance and with product- and process-related impurities.

Although the predictive value of animal models for immunogenicity in humans is considered low, antibody measurements, if applicable, should be included in the repeat-dose toxicity study to aid in the interpretation of the toxicokinetic data and in assessing, as part of the overall comparability exercise, whether important differences in structure or immunogenic impurities exist between the SBP and the RBP (the immunological response may be sensitive to differences not detected by laboratory analytical procedures).

Depending on the route of administration, local tolerance may need to be evaluated. If feasible, this evaluation may be performed as part of the described repeat-dose toxicity study.
On the basis of the demonstration of similarity between the SBP and RBP by the additional comparability exercise performed as part of the quality evaluation, other routine toxicological studies – such as safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies – are not generally requirements for the nonclinical testing of an SBP, however when the results of the repeat-dose toxicity or the local tolerance study and/or by other known toxicological properties of the RBP (e.g. known adverse effects of the RBP on reproductive function) study reveal the need, it should be done.

Reference:

i. Refer to **ICH S6:** Preclinical safety evaluation of biotechnology-derived pharmaceuticals.
ii. WHO TRS 977 Annex *2*

7.0 MODULE 5: CLINICAL STUDY

The requirements for documentation of the clinical data depend on the existing knowledge about the reference product and claimed therapeutic indications.

The submission must include the information demonstrating that there are no clinically meaningful differences between the SBPs and the RBPs in term of Safety, Quality and Efficacy.

Clinical programs for a SBPs application should be conducted in a facility which is Good Clinical Practice (GCP) compliant and a certificate issued by regulatory Authority from the country of origin and/or competent regulatory Authority should be present in the submission.

The clinical comparability exercise should include pharmacokinetics (PK), Pharmacodynamics (PD) studies followed by Clinical Efficacy and Safety trials.

Further guidance on statistical considerations and extrapolations of indications can be obtained in WHO guidelines on evaluation of similar biotherapeutic product,2013.

7.1 Pharmacokinetic (PK) studies

Comparative pharmacokinetic studies should be conducted to demonstrate the similarities in pharmacokinetic (PK) parameters between SBPs and the RBPs.

(a) If appropriate from an ethical point of view, healthy volunteers will in most cases represent a sufficiently sensitive and homologous model for such comparative PK studies.
(b) Choice of designs must be justified and should consider factors such as clearance and terminal half-life, linearity of PK parameters, where applicable, the endogenous level and diurnal variations of the product under study, production of neutralizing antibodies, conditions and diseases to be treated.

(c) The acceptance criteria to conclude clinical comparability should be defined prior to the initiation of the study, taking into consideration known PK parameters and their variations, assay methodologies, safety and efficacy of the RBPs.

(d) Other PK studies such as interaction studies or PK studies in special populations (e.g. children, elderly, and patients with renal or hepatic insufficiency) shall be submitted.

7.2 Pharmacodynamics (PD) studies

Pharmacodynamics (PD) markers should be selected on the basis of their relevance to demonstrate therapeutic efficacy of the product. If direct PD markers are not practical a surrogate marker which is clinically validated may be employed.

The Pharmacodynamic effects of the SBPs and the RBPs should be compared in a population where the possible differences can be best observed.

Design and duration of the studies must be justified. The PD study may be combined with a PK study and the PK/PD relationship should be characterized so as to provide information on relationship between exposure and effects.

The selected dose should in the steep part of the dose-response curve. Studies at more than one dose may be useful.

Reference:

i. ICH E 10: Choice of control group and related issues in clinical trials: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf.

7.3 Clinical efficacy trials

Comparative clinical trials (head-to-head adequately powered, randomized, parallel group clinical trials, so-called equivalence trials") are required to demonstrate the

similarity in the efficacy and the safety profiles between the SBPs and the RBPs. Assay sensitivity must be ensured (refer to ICH E10).

Equivalence margins should be pre-specified and adequately justified on clinical grounds. Equivalent rather than non-inferior efficacy should be shown in order for the SBPs to adopt the posology of the RBPs and to open the possibility of extrapolation to other indications, which may include different dosages.

Clinical studies should be designed to demonstrate comparable safety and efficacy of the SBP to the reference product and therefore need to employ testing strategies that are sensitive enough to detect relevant differences between the products, if present.

7.4 Clinical safety and effectiveness

Similar efficacy will usually have to be demonstrated in adequately powered, randomized and controlled clinical trials(s). Clinical studies should preferably be double-blind or at a minimum observed blind. Furthermore, a sensitive and preferably well-established clinical model is required. Equivalence trials are clearly preferred for comparison of the SBP with the reference product. Non-inferiority designs may be considered if appropriately justified.

Even if the efficacy is shown to be comparable, the similar biotherapeutic medicinal product may exhibit a difference in the safety profile (in terms of nature, seriousness, or incidence of adverse reactions). Thus, data from a sufficient number of patients and adequate study duration with sufficient statistical power to detect major safety and effectiveness differences are needed.

Data from pre-approval studies are insufficient to identify all these differences in safety. Therefore, applicant should submit a risk management plan/pharmacovigilance plan for the SBPs. The plan must be with the intention to mitigate potential risks associated to the SBPs. Also, the submission should address the strategy to execute the plan.

For products intended for use for more than 6 months, the size of the safety database should typically conform to the recommendations of ICH E1.

Reference:

i. ICH E1: The extent of population exposure to assess clinical safety for drug intended for long term treatment for non-life threatening conditions: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

7.5 Clinical Immunogenicity

Immunogenicity of SBPs should be investigated prior to Marketing Authorization. Structural and functional studies as well as animal data are generally not adequate to predict immunogenicity in humans. Therefore, at least one clinical study that includes a comparison of the immunogenicity of the proposed SBPs to that of the RBPs in humans has to be submitted. The data should be submitted so as to evaluate potential differences between the proposed SBPs and the RBPs in the incidence and severity of human immune responses.

A written rationale on the strategy for testing immunogenicity should be provided.

EAC recommends that immunogenicity assays be developed and validated with respect to both the proposed SBPs and RBPs product early in development. Validated assays/methods should be used for testing immunogenicity with appropriate specificity and sensitivity.

Special attention should be given to the possibility that the immune response seriously affects the endogenous protein and its unique biotherapeutic product function and thus leads to adverse reactions.

The proposed SBPs and RBPs should be evaluated in the same clinical trial of sufficient duration with the same patient sera whenever possible. The duration of the study should be defined on a case –to case basis using appropriate route of administration by comparative parallel designs. At the time of submission, the study should have covered at least 6 months or and if less, should be scientifically justified.

Note:
Data at the end of the 12 months should be presented as part of the post-marketing commitment.

In situations where an applicant is seeking to extrapolate immunogenicity data for one indication to other indications, the applicant should consider using the population and regimen for the RBPs for which development of immune responses with adverse outcomes is most likely to occur.

The selection of clinical immunogenicity endpoints or PD parameters linked to immune responses (e.g., antibody formation and cytokine levels) should take into consideration the immunogenicity issues that have emerged during the use of the RBPs. The clinical immune response criteria should be defined, using established criteria where available, for each type of potential immune responses.

Reference:

i. CHMP Guideline on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins (CHMP/BMWP/14327/06).

A warning statement on the risks associated with switching of products during treatment, and against product substitution, is to be included in the package insert of the SBPs. This should be done by prescriber.

Reference:

i. Guidelines for non-clinical and clinical development of similar biotherapeutic medicinal products containing recombinant erythropoietin (EMA/CHMP/BMWP/3016636/2008).

ii. Guidelines for non-clinical and clinical development of similar biotherapeutic product medicinal products containing recombinant human insulin and insulin analogues (EMA/134217/2012).

iii. Guidelines for non-clinical and clinical development of similar biotherapeutic medicinal products containing recombinant Granulocyte Colony Stimulating factor (rG-CSF_) (EMEA/CHMP/BMWP/31329/2005).

iv. Guidelines for non-clinical and clinical development of similar biotherapeutic medicinal products containing low-molecular-weight-heparins (EMEA/134870/2012).

v. Guidelines for non-clinical and clinical development of similar biotherapeutic medicinal products containing recombinant alfa-containing medicinal products (EMEA/CHMP/BMWP/102046/2006).

vi. Guidelines for non-clinical and clinical development of similar biotherapeutic medicinal products containing recombinant beta-containing interferon beta-containing medicinal products (EMEA/CHMP/BMWP/652000/2010).

vii. Guidelines for non-clinical and clinical development of similar biotherapeutic medicinal products containing monoclonal antibodies- (EMEA/CHMP/BMWP/403543/2010).

7.6 Pharmacovigilance

As for most biotherapeutic medicinal product, data from pre-authorization clinical studies are usually too limited to identify all potential unwanted effects of an SBP. In

particular, adverse events are unlikely to be encountered in the limited clinical trial populations being tested with the SBP. Further close monitoring of the clinical safety of an SBP in all approved indications and a continued benefit-risk assessment are therefore necessary in the post-marketing phase.

The manufacturer should submit a Periodic Benefit-Risk Evaluation Report (PBRER) and pharmacovigilance plan/risk management plan at the time of submission of the marketing authorization application. The principles of pharmacovigilance planning can be found in relevant guidelines such as ICH E2E.

Reference:

i. ICH E2E (Pharmacovigilance Planning): http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf

APPENDIX 1: APPLICATION FORM FOR MARKETING AUTHORIZATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS (SBPs)

1. For official use only (highlighted portion).

Application Number	Official use only
Date of submission of the dossier	Official use only
MODULE 1: ADMINISTRATIVE INFORMATION	
1.0 PARTICULARS OF THE PRODUCT	
1.1	Type of the medicinal product application New SBP Renewal* * If variation has been made, information supporting the changes should be submitted. See variation guidelines for registered medicinal products.
1.2	Proprietary Name
1.3	International Non-proprietary Name (INN) of the Drug substance
1.4	Strength of Drug substance per unit dosage form:
1.5	Name and address (physical and postal) of Applicant
(Company) Name: Address: Country: Telephone: Telefax: E-Mail:	
	Name and address (physical and postal) of Local Technical Representative:
(Company) Name: Address: Country: Telephone: Telefax: E-Mail:	
1.6	Pharmaceutical Dosage form* and route of administration* * List of standard terms for dosage forms and routes of administration is available on Guidelines on List of Standard Terms for Pharmaceutical Dosage Forms and Routes of Administration.
1.6.1	Dosage form:
1.6.2	Route(s) of administration (use current list of standard terms)
1.7	Packing/pack size:
1.8	Visual description

	(Add as many rows as necessary)
1.9	Proposed shelf life (in months):
1.9.1	Proposed shelf life (after reconstitution or dilution):
1.9.2	Proposed shelf life (after first opening container):
1.9.3	Proposed storage conditions:
1.9.4	Proposed storage conditions after first opening:
1.10	Other sister medicinal products registered or applied for registration
1.10.1	Do you hold Marketing Authorization (s) of other medicinal product (s) containing the same active pharmaceutical ingredient(s) in the EAC? If yes state; ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Partner States where product is authorized: ▪ Marketing authorization number(s): ▪ Indication(s):
1.10.2	Have you applied for Marketing Authorization medicinal product(s) containing the same drug substance (s) in the EAC? ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Indication(s):
1.11	Pharmacotherapeutic group and ATC Code
1.11.1	Pharmacotherapeutic group:
1.11.2	ATC Code: (Please use current ATC code)
1.11.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐
1.12	Distribution category: Controlled Drug ☐ POM ☐ Pharmacy Only ☐ OTC ☐ General sale ☐ (Applicants are invited to indicate which categories they are requesting, however, the Authority reserve the right to change and/or apply only those categories provided for in their national legislation)
1.13	Country of origin:
1.14	Product Marketing Authorization in the country of origin (Attach Certificate of Pharmaceutical Product from National Medicines Regulatory Authority). If not registered, state reasons

☐Authorized Country: Date of authorization (dd-mm-yyyy): Proprietary name: Authorization number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	☐ Withdrawn (by applicant after authorization) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: ☐ Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name:

1.15	List ICH countries and Observers where the product is approved.
1.16	Name(s) and complete physical address(es) of the manufacturer(s)
1.16.1	**Name(s) and physical address (es) of the manufacturing site of the drug product, including the final product release if different from the manufacturer. Alternative sites should be also declared here.** All manufacturing sites involved in the manufacturing process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed. (Add as many rows as necessary
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.16.2	**Name(s) and physical address(es) of the manufacturer(s) of the drug substance** (Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites should be listed.
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.18	Name and address (physical and postal) of the person or company responsible for Pharmacovigilance
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.19	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph e.t.c. used for Drug Product.

1.20	Qualitative and Quantitative composition of the drug substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g. 1 capsule).

Name of drug substance(s)*	Quantity / dosage unit	Unit of measure	Reference/ monograph standard	
1.				
2.				
e.t.c				
Name of excipient(s)				
1.				
2.				
e.t.c				

Note: * Only one name for each substance should be given in the following order of priority: INN**, Pharmacopoeia, common name, scientific name

** The drug substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.

Details of averages should not be included in the formulation columns but should be stated below:

- Drug substance(s):
- Excipient(s):

1.21	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

Name and address (physical and postal) of the site(s) where the non- clinical studies of the product were conducted

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

2.0 DECLARATION BY AN APPLICANT

I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge.

I..... the undersigned certify that all the information in this form and all accompanying documentation is correct. I further certify that I have examined the following statements and I attest to their correctness: -

a) The current edition of the **"**EAC Compendium of Good Manufacturing Practices"
b) The formulation per dosage form correlates with the master formula and with the batch manufacturing record.
c) The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record.
d) Each batch of all starting materials is either tested or certified (in accompanying certificate of analysis for that batch) against the full specifications in the accompanying documentation and must comply fully with those specifications before it is released for manufacturing purposes.
e) All batches of the drug substance(s) are obtained from the source(s) specified in the accompanying documentation.
f) No batch of drug substance will be used unless a copy of the batch certificate established by the manufacturer is available.
g) Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before released for the manufacturing purposes.
h) Each batch/lot of the SBPs is either tested, or certified (in an accompanying certificate of analysis for that batch), against the full specifications in the accompanying documentation and complies fully with release specifications before released for sale.
i) The person releasing the product is an authorized person as defined by the "EAC Compendium of Good Manufacturing Practices".
j) The procedures for control of the Drug product have been validated. The assay method has been validated for accuracy, precision, specificity and linearity.
k) All the documentation referred to in this application is available for review during GMP inspection.
l) Non-clinical and clinical data were conducted in accordance with Good Clinical Practice,

I also agree that:

(a) As holder of registration I will adhere to requirements for handling batch recalls of the products. I also agree that I shall carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports to the

Authority.

(b) I further agree that I am obliged to follow the requirements of the Legislations and Regulations, which are applicable to medicinal products.

(c) I also consent to the processing of information provided by the Authority.

(d) It is hereby confirmed that fees will be paid/have been paid according to the Fees and Charges Regulations in force.

Name:
Qualification:
Position in the company:
Signature:
Date: **Official stamp:**

APPENDIX 2: PUBLIC ASSESSMENT SUMMARY INFORMATION FOR SIMILAR BIOTHERAPEUTIC PRODUCT

< Name of the SBP**>**
<Tanzania Food and Drugs Authority (TFDA); Date…… >

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	SBP **Information**	
MAH	**Name of the Similar Biotherapeutic Product**	< Invented/Trade name >
MAH	**MAH**	Name and address
MAH / TFDA	**Active ingredient manufacturing facilities and batch release site for the finished product** (if applicable)	< Name(s) and address(es) > < Confidential – Not Released >
MAH	**Name of the active ingredient(s)**	(INN/ Common name/ Local name/ BQ if applicable)
MAH	**Pharmaco-therapeutic group**	e.g. ATC code
MAH	**Substance category**	As described in WHO INN guidance: WHO/EMP/RHT/TSN/2014.1
MAH	**Pharmaceutical form**	Standard Term
MAH	**Quantitative composition**	Strength
MAH	**Route of administration**	Route
MAH	**Packaging/material**	Primary container
MAH	**Package size(s)**	Presentations available
MAH	**Local legal basis**	Legislative Reference
MAH	**Local Similar**	Reference to applicable guidelines

	Biotherapeutic Productguidelines	
TFDA	**Date of authorisation/licensing of Similar Biotherapeutic Product**	Approval date for SBP
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Trade name of reference biotherapeutic product
MAH	**Authorised indications for RBP**	Indications approved for reference biotherapeutic product in full or summary + English reference
MAH	**Quantitative Composition/ Pharmaceutical form/ Route of administration (of RBP)**	As detailed
MAH	**Authorisation (Licence) number (of RBP)**	Registration number(s) of the RBP
MAH	**Date of authorisation (of RBP)**	Approval date(s) for reference biotherapeutic product
MAH	**Authorisation (Licence) Holder (of RBP)**	Company name of licence holder
MAH	**Source of RBP (or other comparator) for comparability exercise**	Region(s) where reference biotherapeutic product has been acquired in order to perform biosimilarity exercise.
MAH / TFDA	**Availability of the RBP assessment report** (language)/**link**	Provide link to public assessment report in English for reference biotherapeutic product
	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	High level summary of data included in comparability exercise for biosimilarity.
TFDA	**Interchangeability with the RBP**	Confirm yes / comments (any

	(has interchangeability been approved for this product?)	additional data are specified in Part B, below)
TFDA	**Availability of full assessment report** (language)/**link**	Provide link to main public assessment report for SBP
MAH	**Indications applied for** (if different to RBP)	Summary of indications requested in biosimilar application
TFDA	**Authorised indications for Similar Biotherapeutic Product**	Indications approved following review – in full or if available in English on TFDA website: provide summary and link.
MAH (Marketing Authorisation Holder)		
TFDA (Tanzania Food and Drugs Authority)		

PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
MAH	**Quality data. Composition of the** SBP**(s)**
	Provide name of active substance and strength. Provide names (qualitative) of excipients used in formulation.
MAH	**Quality data. State-of-the-art methods**
	Include high level summary of physicochemical test methods and biotherapeutic product activity studies used for characterisation.
CA	**Quality data assessment outcome**
	Provide high level summary review of comparability data. Specify any differences requiring additional assurance and outcome (any differences? If yes, why it was not considered to affect quality, efficacy or safety of the product?).
MAH	**Mechanism of action**
	Describe mechanism of action relevant to indications applied for.
MAH	**Nonclinical data. *In vitro* studies**
	Specify dose used and length of the study.
MAH	**Nonclinical data. *In vivo* studies**

	Specify animal model(s), e.g. dose used and length of the study.
CA	**Nonclinical data assessment outcome**
	Provide high level summary review of nonclinical data and outcome (any differences? If yes, why it was not considered to affect efficacy or safety of the product?).
	CLINICAL STUDIES **- include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.** • **Pharmacokinetic, PK** • **Pharmacodynamic, PD** • **Efficacy,** • **Safety,** • **Immunogenicity.**
MAH	**Clinical data. PK studies**
	Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study.
CA	**Clinical data. PK data assessment outcome**
	Provide high level summary review of PK data and outcome (any differences? If yes, why it was not considered to affect efficacy or safety of the product?).
MAH	**Clinical data. PD studies**
	Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study.
CA	**Clinical data. PD data assessment outcome**
	Provide high level summary review of PD data and outcome (any differences? If yes, why it was not considered to affect efficacy or safety of the product?).
MAH	**Clinical data. Efficacy studies**
	Specify study number(s) and summary of design, population, objective and endpoint (e.g. equivalence margins), dose used and length of the study.
CA	**Clinical data. Efficacy data assessment outcome**
	Provide high level summary review of clinical efficacy data and outcome (No

	differences expected, however, justification may be appropriate).	
MAH	**Clinical data. Safety/ Immunogenicity studies** (specify population, dose used, length of the study and comparability margins)	
	Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the stud(ies).	
CA	**Clinical data. Safety/ Immunogenicity data assessment outcome**	
	Provide high level summary review of clinical safety and immunogenicity data and outcome (No differences expected, however, justification may be appropriate). Safety. ADRs were <not> observed. <The ADRs were equivalent to the ADRs observed with the RBP.><The ADRs were different from the ADRs observed with the RBP.> Immunogenicity. Antibody formation in < SBP> was considered to be comparable to that in the RBP, using appropriately validated methods.	
MAH	**Interchangeability with the RBP**	
	(If legislation applicable to your Authority allows interchangeability, specify any additional date that has been provided, as appropriate)	
MAH	**Additional information about the comparability exercise**	As appropriate, if not previously included.
MAH	**Post-authorization measures**	
	Is a risk management plan available? Which Q/ S/ E studies are included?	
CA	**Post-authorization measures assessment outcome.**	
	< The risk management plan (or equivalent) was considered to be acceptable. > < No additional risk management activities are foreseen post-approval.>	
MAH	**Availability of additional relevant information in the local language/ link**	As required /appropriate

PART C - REVIEWER CONCLUSIONS	
CA	**Conclusions on biosimilarity, approval, interchangeability**

The reviewer should comment and conclude on the followings:- <The data provided by the Applicant were in line with the local legislation and guidelines.> <The data provided by the Applicant were in line with the local legislation, guidelines and international guidelines.> <u>Quality</u> All major physicochemical characteristics and biotherapeutic product activities of < SBP trade name > were comparable to those of the reference biotherapeutic product <trade name >. <u>Nonclinical</u> No major differences in nonclinical data were observed for <biosimilar product trade name > compared to the reference biotherapeutic product <trade name >. <u>Clinical Studies</u> The PK / PD / efficacy studies to demonstrate biosimilarity conducted in < patient poulation> provided robust evidence of therapeutic equivalence versus the reference biotherapeutic product <trade name >. Additional data were provided < in another indication> to support biosimilarity / demonstrate interchangeability. Safety: The ADRs observed with <biosimilar product trade name > were in the same range as the ADRs observed with the reference biotherapeutic product <trade name >. Immunogenicity: The proportion of patients who developed anti-drug antibodies (ADA) with <biosimilar product trade name > was generally similar for the reference biotherapeutic product <trade name >. <u>Risk Management</u> < The risk management plan (or equivalent) was considered to be acceptable. > < No additional risk management activities are foreseen post-approval.> <u>Overall Conclusion</u> <Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise> <Concerns raised during the review relating to < summarise major issues > were resolved during the procedure.> The biosimilar product <trade name > was considered approvable. The biosimilar product <trade name > was considered to be interchangeable with the	

reference biotherapeutic product <trade name >.

<Name of the biosimilar medicinal product>

<Competent Authority (NRA)>

<APPROVED / NOT APPROVED>

PART A - ADMINISTRATIVE INFORMATION		
Entered by:	**Biosimilar Product Information**	
MAH	**Name of the biosimilar medicinal product**	< Invented/Trade name >
MAH	**MAH**	Name and address
TFDA	**Authorisation / Licence number**	< local authorisation number >
MAH / TFDA	**API manufacturing facilities and batch release site for the finished product** (if applicable)	< Name(s) and address(es) > < Confidential – Not Released >
MAH	**Name of the active substance**	(INN/ Common name/ Local name/ BQ if applicable)
MAH	**Pharmaco-therapeutic group**	e.g. ATC code
MAH	**Substance category**	As described in WHO INN guidance: WHO/EMP/RHT/TSN/2014.1
MAH	**Pharmaceutical form**	Standard Term
MAH	**Quantitative composition**	Strength
MAH	**Route of administration**	Route
MAH	**Packaging/material**	Primary container
MAH	**Package size(s)**	Presentations available

MAH	**Local legal basis**	Legislative Reference (Indicate which regulatory pathway has been used to approve the product)
MAH	**Local biosimilar guidelines**	Reference to applicable guidelines
MAH	**Date of authorisation/licensing of biosimilar**	Approval date for biosimilar
	Reference Biotherapeutic Product (RBP) Information	
MAH	**Name of the RBP**	Trade name of reference biotherapeutic product
MAH	**Authorised indications for RBP**	Indications approved for reference biotherapeutic product in full or summary + English reference
MAH	**Pharmaceutical form**	As detailed in RBP label
MAH	**Quantitative composition**	As detailed in RBP label
MAH	**Route of administration**	As detailed in RBP label
MAH	**Packaging/material**	Primary container
MAH	**Package size(s)**	Presentations available (include as appropriate)
MAH	**Authorisation (Licence) number (of RBP)**	Local (e.g. NCA) code for reference biotherapeutic product
MAH	**Date of authorisation (of RBP)**	Approval date for reference biotherapeutic product
MAH	**Authorisation (Licence) Holder (of RBP)**	Company name of licence holder
MAH	**Source of RBP (or other comparator) for comparability exercise**	Region(s) where reference biotherapeutic product has been acquired in order to perform biosimilarity exercise.
MAH / TFDA	**Availability of the RBP assessment report** (language)/**link**	Provide link to public assessment report in local language for reference biotherapeutic product

	Summary of outcomes	
MAH	**Comparability exercise to demonstrate similarity to RBP**	High level summary of data included in comparability exercise for biosimilarity.
TFDA	**Availability of full assessment report** (language)/**link**	Provide link to main public assessment report for biosimilar product
MAH	**Indications applied for** (if different to RBP)	Summary of indications requested in biosimilar application
TFDA	**Authorised indications for biosimilar**	Indications approved following review – in full or if available in English on NRA website: provide summary and link.

MAH (Marketing Authorisation Holder) or Sponsor
TFDA (Tanzania Food and Drugs Authority)

PART B - SUBMITTED DATA AND REVIEWER SUMMARY	
Procedure: <Initial Application><Variation / Supplement> <Variation number and scope: [Quality / Safety / Efficacy / Risk Management] and description>	
MAH	**Quality data. Composition of the biosimilar product(s)**
	Provide name of active substance and strength. Provide names (qualitative) of excipients used in formulation.
MAH	**Quality data. State-of-the-art methods**
	Include high level summary of physicochemical test methods and biotherapeutic product activity studies used for characterisation (Tables may be used for clarity).
TFDA	**Quality data assessment outcome**
	Provide high level summary review of comparability data. Specify any differences requiring additional assurance and outcome (any differences? If yes, why it was not considered to affect quality, efficacy or safety of the product? i.e. including the underlying scientific assessment).
MAH	**Mechanism of action**
	Describe mechanism of action relevant to indications applied for.
MAH	**Nonclinical data. *In vitro* studies**

	Specify dose used and length of the study.
MAH	**Nonclinical data. *In vivo* studies**
	Specify animal model(s), e.g. dose used and length of the study.
TFDA	**Nonclinical data assessment outcome**
	Provide high level summary review of nonclinical data and outcome (any differences? If yes, why it was not considered to affect efficacy or safety of the product? i.e. including the underlying scientific assessment).
	CLINICAL STUDIES **- include relevant study data from the following (not all may be required) which have been included to demonstrate biosimilarity.** • **Pharmacokinetic, PK** • **Pharmacodynamic, PD** • **Efficacy,** • **Safety,** • **Immunogenicity.**
MAH	**Clinical data. PK studies**
	Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study.
TFDA	**Clinical data. PK data assessment outcome**
	Provide high level summary review of PK data and outcome (any differences? If yes, why it was not considered to affect efficacy or safety of the product?).
MAH	**Clinical data. PD studies**
	Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study.
TFDA	**Clinical data. PD data assessment outcome**
	Provide high level summary review of PD data and outcome (any differences? If yes, why it was not considered to affect efficacy or safety of the product?).
MAH	**Clinical data. Efficacy studies**
	Specify study number(s) and summary of design, population, objective and

	endpoint (e.g. equivalence margins), dose used and length of the study.	
TFDA	**Clinical data. Efficacy data assessment outcome**	
	Provide high level summary review of clinical efficacy data and outcome (No differences should be seen, however, justification may be appropriate for minor differences). Provide summary of scientific evidence leading to decision on extrapolation.	
MAH	**Clinical data. Safety/ Immunogenicity studies** (specify population, dose used, length of the study and comparability margins)	
	Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the stud(ies).	
TFDA	**Clinical data. Safety/ Immunogenicity data assessment outcome**	
	Provide high level summary review of clinical safety and immunogenicity data and outcome (No differences should be seen, however, justification may be appropriate for minor differences). <u>Safety</u>. ADRs were <not> observed. <The ADRs were equivalent to the ADRs observed with the RBP.><The ADRs were different from the ADRs observed with the RBP.> <u>Immunogenicity</u>. Antibody formation in <biosimilar product> was considered to be comparable to that in the RBP, using appropriately validated methods.	
MAH	**Interchangeability data**	
	(If legislation applicable to your Authority allows interchangeability, specify any additional data that has been provided, as appropriate) OR state < No additional data were provided >	
MAH	**Additional information about the comparability exercise**	As appropriate, if not previously included.
MAH	**Post-authorization measures**	
	Is a risk management plan available? Which Q/ S/ E studies are included?	
TFDA	**Post-authorization risk measures: assessment outcome.**	
	< The risk management plan (or equivalent) was considered to be acceptable. > < No additional risk management activities are foreseen post-approval.>	

MAH	**Availability of additional relevant information in the local language/ link**	As required /appropriate

PART C - REVIEWER CONCLUSIONS	
TFDA	**Conclusions on biosimilarity, approval**

The data provided by the Applicant were in line with the local legislation and guidelines.
<The data provided by the Applicant were in line with the local legislation, guidelines and international guidelines.>

Quality
The SBP manufacturer has developed and validated a process capable of consistently manufacturing a product of appropriate quality, with satisfactory control of impurities. Manufacturing operations are carried out according to cGMP requirements.

The quality attributes of high relevance for clinical safety and efficacy, e.g. physicochemical characteristics and biotherapeutic product activities of <biosimilar product trade name > were comparable to those of the reference biotherapeutic product <trade name >.

Nonclinical
No major differences in nonclinical data were observed for <biosimilar product trade name > compared to the reference biotherapeutic product <trade name > .

Clinical Studies

The PK / PD / efficacy studies to demonstrate biosimilarity conducted in < patient population> provided robust evidence there are no clinically meaningful differences versus the reference biotherapeutic product <trade name >.

Additional data were provided < in another indication> to support biosimilarity / demonstrate interchangeability (this summary report may not include decision in interchangeability).

Safety: The ADRs observed with <biosimilar product trade name > were in the same range as the ADRs observed with the reference biotherapeutic product <trade name >.

Immunogenicity: The proportion of patients who developed anti-drug antibodies (ADA) with <biosimilar product trade name > was generally similar for the reference biotherapeutic product <trade name >.

Extrapolation of indications: Based on the totality of evidence, all indications requested for <biosimilar product trade name > (see Section A, summary of outcomes) were considered to be approvable.
< Due to a lack of assurance concerning <quality / nonclinical / clinical > data, the indication(s) < enter summary of non-approvable indications > were not granted for <biosimilar product trade name >.

Risk Management
The risk management plan (or equivalent) was considered to be acceptable.
< No additional risk management activities are foreseen post-approval.>

Overall Conclusion
Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise.
<Concerns raised during the review relating to < summarise major issues > were resolved during the procedure.>

The biosimilar product <trade name > was considered approvable.

<< The NCA has determined that the biosimilar product <trade name > was considered to be interchangeable with the reference biotherapeutic product<trade name > .

References:

1. World Health Organization (WHO) Guidelines on Evaluation of Similar Biotherapeutic Products (SBP), 2013.

2. WHO Guidelines on the Quality, Safety, and Efficacy of biotherapeutic protein products prepared by recombinant DNA technology, June 2013.

3. FDA-Scientific Considerations in Demonstrating Biosimilarity to a Reference Product.