EAST AFRICAN COMMUNITY

EAC GUIDELINES FOR REGISTRATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS

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PREFACE

The East African Community (EAC) Partner States' National Medicine Regulatory Authorities (NMRAs) requires that all medicinal products intended to be marketed in their respective countries 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). This Guideline is made to provide guidance to applicants on the procedure for registering a Similar Biotherapeutic Product in EAC countries.

These 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.

This document is intended to provide guidance on issues to consider when demonstrating that a proposed biological product is similar to, a reference biotherapeutic product already registered, well established for purposes of submitting a marketing application.For the purpose of this document, a Similar Biotherapeutic Product (a short designation for highly similar biological medicinal product) is considered as a new biological medicinal product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, medicinal product. Similar Biotherapeutic Products are not generic biologics hence they should be submitted as new products**.**

The EACPartner States' NMRAs will evaluate Similar Biotherapeutic Products before they are registered in EAC countries and monitor the products once they are on the market. The region will also assess the suitability of Similar Biotherapeutic Products for export from EAC countries.

Submission of satisfactory comparability data on the quality, safety, and efficacy of the Similar Biotherapeutic Product to the Reference Biotherapeutic Product will enable EAC

to assess the suitability of the product for its intended use in EAC countries. Applicants are therefore encouraged to acquaint themselves with this document before completing the registration form. These guidelines should be read in conjunction with EAC Guideline for the Registration of Biotherapeutic products. The EAC region is also working with other competent authorities towards harmonization of guidelines used to evaluate and register Similar Biotherapeutic Products.

Marketing Authorization Holders as well as other stakeholders are encouraged to provide comments for improvement based on their experience on the use of these guidelines.

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
WHO	-	World Health Organization

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 substances (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 adefined 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 biological 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 biological 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.

“ICH” means International council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonization in the interpretation and application of technical guidelines and requirements for product registration in order to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines. For more information, see http://www.ich.org/.

“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. Generally, genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body.

“Pharmacopoeias” means a current edition of British Pharmacopoeia, (BP), European Pharmacopoeia, (Ph. Eur), International Pharmacopoeia, (IP), 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. The decision to approve a drug is based on a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient populations and the number of patients exposed. In particular, during the early post-

marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use.

“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. It does not refer to measurement standards such as international, pharmacopoeial, or national standards or reference standards.

“Similar Biotherapeutic Product” means a new 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. The requirements for the registration of similar biotherapeutic product are based on the demonstration of similarity (i.e. no clinically meaningful difference between the similar biotherapeutic product and the reference biotherapeutic product) in terms of quality, safety and efficacy to an already registered, reference biological product.

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

“Similarity” means if a company chooses to develop a new biological 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 new similar biological 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.

“Variation” means a change in the indication(s), dosage recommendation(s), drug classification and/or patient group(s) for a previously registered drug being marketed under the same name in Tanzania. A variation also includes, but is not limited to, a change in the product name, site of manufacture and/or source of ingredients.

“Well-characterized biologic” A well-characterized biologic is a chemical 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 biological 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

Biotherapeutics are molecules derived from biotechnology methods or other cutting-edge technologies. They were introduced on the market in the early 1980s, setting new milestones in modern pharmaceutical therapy that improve quality of life for many patients with life-threatening, serious, chronic and debilitating diseases.

Biotherapeutic products are large, highly complex molecular entities manufactured using living cells and are inherently variable. The manufacturing process is highly complex and critical to defining the characteristics of the final product. Maintaining batch-to-batch consistency is a challenge. Subtle variations in the production or even transport or storage conditions may potentially result in an altered safety and efficacy profile of the final product.

Based on the current analytical techniques, two biologics produced by different manufacturing processes cannot be shown to be identical, but similar at best. Therefore, the term Similar Biotherapeutic Products (SBP) is appropriate. Immunogenicity of SBP is of concern from clinical and safety perspective. Clinical trials and a robust post-market surveillance/pharmacovigilance plan are essential to guarantee that the product is safe and efficacious over time.

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 a proposed SBP. The marketing application must include information demonstrating biosimilarity, based on data derived from, among other things, analytical studies that demonstrate that the biological is highly similar to the RBP notwithstanding minor differences in clinically inactive components.

Although the regulatory framework applies generally to biological products, this guidance document focuses on SBP and provides an overview of the quality, non-clinical and

clinical factors to consider in demonstrating bio similarity between a proposed biological product and the reference product.

SBPs can be approved based in part on an exercise to demonstrate similarity to an already approved RBP. 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 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.

References:

WHO TRS 977, Annex 2, i.e. WHO biosimilar guidelines

1.1 THE CONCEPT OF SIMILAR BIOTHERAPEUTIC PRODUCTS

The concept of a Similar Biotherapeutic Product (SBP) applies to biological 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 that biotherapeutic products claimed to be highly similar to a reference product do 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 biologics 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, tumour necrosis factors), erythropoietin's, 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 diagnostics.

2: GENERAL INFORMATION

2.1 GENERAL REQUIREMENTS

For general requirements of application for registration of SBPs reference should be made to the EAC guidelines on documentation for registration of biotherapeutic products, available at partner states website by dully filling an application form in annex I.
This guideline also composes of template (Appendix 2) of the Summary Information for Similar Biotherapeutic Product (SIB) of which general information of the components SIB template should be filled out by Marketing Authorization Holder (MAH). The EAC NMRAs will fill out the components which are general for the product summary including the status of the registered product. The SIB will be filled out with dossier of first authorization. For any amendment, SIB will be updated.

SBP submission must follow the format described in EAC Guidelines on documentation for the Registration of Biotherapeutic products. Due to nature of SBP, some CTD sections described in EAC Guideline for the Registration of Biotherapeutic products are not applicable: Thus, guidance is given in this documents. There are some additional requirements, again specific to SBP's, which are described in module 3,4 and 5.

2.2 Consideration for the Choice of RBP

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;

3.1.1 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.

3.1.2 The manufacturer must demonstrate that the chosen RBP is suitable to support the application for marketing authorization of SBP.

3.1.3 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.

3.1.4 The same RBP should be used throughout the development of the SBP (i.e. throughout the comparative quality, nonclinical, and clinical studies).

3.1.5 The active ingredient of the RBP and the SBP must be shown to be similar.

3.1.6 The dosage form and route of administration of the SBP should be the same as that of the RBP.

3.1.7 The following factors should be considered in the choice of an RBP that is marketed in another jurisdiction:

3.1.7.1 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.

3.1.7.2 The acceptance of an RBP for evaluation of an SBP does not imply that the EAC Partner States 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.

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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 biological 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 biological product.

d) Risk management/pharmacovigilance plans

2.4. OTHER REQUIREMENTS

2.4.1 Manufacturer's declaration

A 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 biological product that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application.

The applicants intending to develop SBPs should meet with regulators in their country of origin to present their product development plans and establish a schedule of milestones that will serve as standards for future discussions with the respective regulators.

2.4.2. Expert Report

Experts must provide detailed 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:

i. The Quality Overall Summary, Non-clinical Overview/Summary and
ii. Clinical Overview/Summary
iii. A declaration signed by the experts
iv. 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.

2.5. SCIENTIFIC GUIDELINES APPLICABLE TO ALL SIMILAR BIOTHERAPEUTIC PRODUCT

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

References:

EMA: http://www.ema.europa.eu

International council of Harmonisation (**ICH**) Guidelines: http://www.ich.org

WHO TRS 977, Annex 2, i.e. WHO biosimilar guidelines, ,

The submission must follow CTD format detailed in EAC Guideline for the Registration of Biotherapeutic products .Followings are requirements specific to SBP dossiers that are submitted for registration

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative information as stipulated in the EAC Guideline for the Registration of Biotherapeutic products.

Summary of Product characteristics (SMPC) for a similar biotherapeutic product should be provided an A4 size and real size copies (both in hard copy and on a CD-ROM in MS-Word of the package insert that contains a Summary of Product Characteristics (SmPC) aimed at medical practitioners and other health professionals using the format outlined below.

Other information on SmPC should be consistent with the RBPs SmPC, any difference in the proposed SmPC vis-à-vis the RBPs SmPC, should be appropriately discussed and justified.

Labelling of biosimilars should be individualized and should clearly indicate which clinical safety and efficacy data have been obtained with the biosimilars. (Data itself should not be included in the label, but studies need to be described). Furthermore, it should clearly be stated that the product is a biosimilar.

This section should follow the EAC Guideline on Summary of Product Characteristics (SmPC)

MODULE 2: OVERVIEW AND SUMMARIES

The purpose of this module is to summarize the quality (chemical, pharmaceutical, and biological), 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 EAC Guideline for the Registration of Biotherapeutic products.

MODULE 3: QUALITY

The information requested under this section should be supplied in format stipulated in the EAC Guideline for the Registration of Biotherapeutic products. The quality part of a SBP, like all other biological products should comply with established scientific and regulatory standards. SBP manufacturer should provide full information on Chemistry, manufacturing and control.

In addition, the SBP manufacturer is required to submit extensive data focused on the similarity, including comprehensive comparative (head – to- head) physicochemical, molecular and biological characterization (these may include bioassays, biological 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 documented.

A summary of the analytical results (these may be in a form of a report) on three consecutive batches of finished product must be provided to support the application for registration. These batches may be pilot or production batches. If they are pilot batches, they must be representative of production batches

3.1 Qualitative and Quantitative Particulars

Qualitative and Quantitative Particulars of SBP shall be presented in a tabular form as indicated in the EAC Guideline for the Registration of Biotherapeutic products.

A list of all components of the SBP and diluents (if applicable) should be given.

The quantities per dose should be stated. A clear description of the active ingredient including the name(s) of the active ingredientshould be provided. The reason(s) for inclusion of each excipient 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.

3.2 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, EAC Guideline for the Registration of Biotherapeutic products, ICH guidelines Q5A, Q5B and Q5D should be referred to.

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 etc should be submitted.

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

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

3.3.2 Characterization of the expression construct, including its genetic stability, should be demonstrated in accordance with principles recommended in **ICH Q5B.**

3.3.3 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.

3.3.4 The full drug master file (DMF), manufacturing process validation protocol and report should be submitted.

3.3.5 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 biological products as prescribed in the EAC Guideline for the Registration 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_guideline/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/Biological Products

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-BiotechnologicalBiological-Products

3.3 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.

3.4 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 [as in **ICH Q2** (**R1**)]

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 must be provided.

Characterizations of a biological product by appropriate techniques, as described in **ICH Q6B** and WHO TRS 987 annex 4 should include the determination of physicochemical properties, biological 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;

ICH Q2 (**R1):** 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

ICH Q6B:*Note for guidance on specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological products*.

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

3.5 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 biological 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.

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

3.6 Product stability

The stability studies should comply with relevant EAC Guidelines for application of Registration for Biotherapeutics, ICH Q5C andQ1A (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;

ICH Q5C - *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products*

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002803.pdf

***Q1A (R2)**–Stability Testing of New Drug Substances and Products*

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073369.pdf

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.

4.1 Special consideration

The design of an appropriate nonclinical study should consider the product characteristics. Results from the physicochemical and biological 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 Registration of Biotherapeutic products and ICH S6, should also be taken into account.

Reference;

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 EAC Guideline for the Registration of Biotherapeutic products

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

a) 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.

b) 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.

4.2 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) Biological/pharmacodynamic activity relevant to the clinical application. These data should usually be available from biological 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, biological activity may be evaluated as part of the nonclinical repeat-dose toxicity study (described below). In-vivo evaluation of biological/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.

4.3 Toxicology

Data on at least repeated dose toxicity conducted in relevant specie should be submitted. Toxicokinetic measurements shall include the following;

4.3.1 Determination and characterization of antibody responses, including anti-product antibody titres

4.3.2 Cross-reactivity with homologous endogenous proteins, and

4.3.3 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.

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

MODULE 5: CLINICALSTUDY

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 programmes 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's on statistical considerations and extrapolations of indications can be obtained in WHO guidelines on evaluation of Similar biotherapeutic product,2013.

5.1 Pharmacokinetic (PK) studies

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

5.1.1 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.

5.1.2 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.

5.1.3 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.

5.1.4 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.

5.2 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;

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

5.3 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.

5.4 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 biological 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;

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

5.5 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 biological 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 at least **12 months** using appropriate route of administration by comparative parallel designs. At the time of submission the study should have covered at least **6 months**.

***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 is to be made to the 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:

EMA guidelines

- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (EMA/CHMP/BMWP/3016636/2008).*

- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMA/134217/2012*

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

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

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

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

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

5.6Pharmacovigilance

As for most biological medicines, 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 inrelevant guidelines such as **ICH E2E.**

Reference:

ICH E2E (Pharmacovigilance Planning)

- http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf

5.7 Appendix 3.2A,3.2R

APPENDIX 1: APPLICATION FORM FOR REGISTRATION 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):

<table>
<tr><td></td><td colspan="2">▪ Partner States where product is authorized:
▪ Marketing authorization number(s):
▪ Indication(s):</td></tr>
<tr><td>1.10.2</td><td colspan="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):</td></tr>
<tr><td>1.11</td><td colspan="2">Pharmacotherapeutic group and ATC Code</td></tr>
<tr><td>1.11.1</td><td colspan="2">Pharmacotherapeutic group:</td></tr>
<tr><td>1.11.2</td><td colspan="2">ATC Code: (Please use current ATC code)</td></tr>
<tr><td>1.11.3</td><td colspan="2">If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐</td></tr>
<tr><td>1.12</td><td colspan="2">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)</td></tr>
<tr><td>1.13</td><td colspan="2">Country of origin:</td></tr>
<tr><td>1.14</td><td colspan="2">Product Marketing Authorization in the country of origin (Attach Certificate of Pharmaceutical Product from National Medicines Regulatory Authority). If not registered, state reasons</td></tr>
<tr><td colspan="2">☐Authorized
Country:
Date of authorization (dd-mm-yyyy):
Proprietary name:
Authorization number:
☐ Refused
Country:
Date of refusal (dd-mm-yyyy):

Reason for Refusal:</td><td>☐ 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:</td></tr>
<tr><td>1.15</td><td colspan="2">List ICH countries and Observers where the product is approved.</td></tr>
<tr><td>1.16</td><td colspan="2">Name(s) and complete physical address(es) of the manufacturer(s)</td></tr>
<tr><td>1.16.1</td><td colspan="2">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</td></tr>
<tr><td colspan="3">Name:
Company name:</td></tr>
</table>

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 further confirm that the information referred to in my application dossier is available for verification during GMP inspection. 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. I further agree that I am obliged to follow the requirements of the Legislations and Regulations, which are applicable to medicinal products. I also consent to the processing of information provided by the Authority. It is hereby confirmed that fees will be paid/have been paid according to the National/Community rules* Name: ……..……. Position in the company:……	

Signature: ……..…… Date:…….. Official stamp:…….. * Note: If fees have been paid, attach proof of payment

Toxicology

(Declare whether toxicology studies have been provided. If not, justify why it should not be required)

Pharmacodynamics (PD) and Pharmacokinetics (PK)

(Declare whether PD & PK studies have been provided.

(Briefly summarize any PD & PK data that have been submitted).

Comparability data

Refer to relevant section on comparability exercise considerations.

Declaration of the Applicant

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 ofGood 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 ofGood 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:

As a holder of marketing authorization/registration of the product I will adhere to EAC requirements for handling adverse reactions.

As holder of registration, I will adhere to EAC requirements for handling batch recalls of the products.

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

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. ICH Guidelines.

4. EMA guidelines : (EMA-Product-specific biosimilar guidelines)

5. FDA-Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product

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