GUIDELINES ON REGISTRATION OF SIMILAR BIOTHERAPEUTIC PRODUCTS

National Drug Authority
Rumee Towers
Plot 19, Lumumba Avenue
P. O. Box 23096
Kampala, Uganda.
Tel: +256 - 0414 - 255665/347391/2
E-mail: ndaug@nda.or.ug
Website: http://www.nda.or.ug

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Adoption and approval of these professional guidelines

In EXERCISE of the powers conferred upon the Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 206 of the Laws of Uganda (2000 Edition), the Drug Authority hereby ADOPTS and ISSUES these Professional **Guidelines on Registration Of Similar Biotherapeutic Products,** Doc. No. PAR/GDL/017, Revision No.:0, made this **7th day of October 2019**,that take effect on **14th October 2019**.

Signature

Dr. Medard Bitekyerezo
CHAIRPERSON
National Drug Authority
Kampala, Uganda

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PREFACE

The National Drug Authority (NDA) requires that all medicinal products intended to be marketed in Uganda meet the acceptable standards of quality, safety and efficacy and be manufactured in facilities that comply with Good Manufacturing Practices (GMP). This Guideline is to provide guidance on the registration requirements for Similar Biotherapeutic Products in Uganda.

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. 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 NDA will evaluate Similar Biotherapeutic Products before they are registered in Uganda and monitor the products once they are on the market. The NDA will also assess the suitability of Similar Biotherapeutic Products for export from Uganda.

Submission of satisfactory comparability data on the quality, safety, and efficacy of the Similar Biotherapeutic Product to the Reference Biotherapeutic Product will enable NDA to assess the suitability of the product for its intended use in Uganda. Applicants are therefore encouraged to acquaint themselves with this document before completing the registration form.

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 Conference on Harmonization
INN	International Non-proprietary Names
MOA	Mechanism of Action
NCE	New Chemical Entity
NDA	National Drug 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.

"Active substance" means an antigenic substance (or compound thereof) that can induce specific responses in humans 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 (or lot): A defined quantity of starting material, packaging material or product processed in one process or series of processes so that it could be expected to be homogeneous. *Note: To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch. In the case of continuous manufacture, the batch shall correspond to a defined fraction of the production, characterised by its intended homogeneity. For the control of the finished product, a batch of a medicinal products comprises of all the units of a pharmaceutical form which are made from the same initial mass of material and have undergone a single series of manufacturing operations or a single sterilisation operation or, in the case of a continuous production process, all the units manufactured in a given period of time.*

"Bioequivalence" means that two pharmaceutical products which are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailabilities, in terms of rate (Cmax and Tmax) and extent of absorption (area under the curve), after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same

"Biotechnology" means a set of tools that employ a living organism (or part of an 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.

"Biotherapeutics" means therapeutic biological products, some of which are produced by recombinant DNA technology.

"Biological products" are medicines that contain a living organism, or are derived from a living organism or biological processes applicable to the prevention, treatment, or cure of a disease or condition of human beings.

"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" refers to head-to-head comparison of a biotherapeutic product with a licensed originator product with the goal of establishing similarity in quality, safety and efficacy. Products should be compared in the same study using the same procedures.

"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" means the dosage form of an immunogenic product in the final immediate packaging intended for marketing.

"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. 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 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" Checks performed during production in order to monitor and if necessary to adjust the process to ensure that the product conforms to its specifications. The control of the environment or equipment may also be regarded as a part of in-process control.

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 the current edition for the time being of any of the following, namely, the International Pharmacopoeia, the British Pharmacopoeia, the British Pharmaceutical Codex, the European Pharmacopoeia, the United States Pharmacopoeia and the British Veterinary Codex

"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.

"Medicinal Product" means an intermediate, drug substance, and/or a drug product, as appropriate.

"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 products 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 Uganda. 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 shall be quantifiable, with impurities being identified if possible; the biological activity and the quantity shall 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 by genetic engineering, 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 Biotherapaeutic Products (SBP) is appropriate. Immunogenicity of SBP is of concern from a clinical and safety perspective. Clinical trials and a robust post-marketing 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 Uganda s, 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 shall include information demonstrating biosimilarity, based on data derived from, among other things, analytical studies that demonstrate that the biologic is highly similar to the Reference Biotherapaeutic Product (RBP) notwithstanding minor differences in clinically inactive components.

Although the regulatory framework applies generally to biological products, this guidance document focuses on SBPs and provides an overview of the quality, non-clinical and clinical factors to consider in demonstrating biosimilarity 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.

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 Objective

The objective of this guideline is to guide the applicants and assessors/regulators on what needs to be submitted to support the registration (marketing authorization) of similar biotherapeutic medicinal products.

1.3 Policy

These guidelines are developed in accordance with:

Section 35(3)(a) and (b) of the National Drug Policy and Authority Act Cap 206, which state that:

"Drug regulation and registration of specialities …If, on application made in the prescribed manner and on payment of the prescribed fee, the authority is satisfied—

(a) that the drug or preparation in respect of which the application is made has not previously been registered; and

(b) that the use of the drug or preparation is likely to prove beneficial, the authority shall register the name and description of that drug or preparation"; and

Section 4(2) of the National Drug Policy and Authority (Registration Regulations, 2014), which states that:

"Registration of drugs, preparations, vaccines and other immunological products. … A person who intends to manufacture, import or export a product shall, prior to the manufacture, importation or exportation of the product, apply to the Authority for registration of the product."

1.4 Scope

These guidelines apply to well-characterized and established molecules (Biotherapeutics), 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), erythropoietins, plasminogen activators, growth hormones and growth factors, insulins, and monoclonal antibodies.

The document does not cover conventional drugs, allergenic extracts, vaccines, blood products, and in vitro diagnostics.

2.0 GENERAL INFORMATION

2.1 General requirements

These guidelines are composed of a template (Appendix 2) of the Summary Information for Similar Biotherapeutic Product (SIB) to be filled by the applicant as specified. The SIB is an accurate record of technical data in the product dossier (PD) at the time of registration and thereafter serves as an official reference document during the course of GMP inspections, variation assessments and renewal of registration assessments as performed by NDA. It represents the final, agreed upon key information from the dossier review.

2.2 Considerations for the choice of RBP

The aim of the SBP approach is to demonstrate close similarity of the SBP in terms of quality, safety and efficacy to a RBP

The following should be considered in selecting RBP;

2.2.1 The RBP should be registered by a stringent regulatory agency (SRA) and 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.

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

2.2.3 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.

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

2.2.5 The active ingredient of the RBP and the SBP shall be shown to be similar.

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

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

a) 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.

b) The acceptance of an RBP for evaluation of an SBP does not imply that the NDA has 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.

Although International Non-proprietary Names (INNs) served as a useful tool in worldwide pharmacovigilance for biologics, they cannot be relied upon as the only means of product identification or as an indicator of the interchangeability of biological products, particularly SBPs.

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.

2.4.2. Expert Report

Experts shall 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:

a) The Quality Overall Summary, Non-clinical Overview/Summary and

b) Clinical Overview/Summary

c) A declaration signed by the experts

d) 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 shall be provided for any additional claims not supported by the dossier.

2.5 Scientific guidelines applicable to all Similar Biotherapeutic products

Applicants are encouraged to refer to product specific guidelines (see section on references) for product specific guidance.

3.0 SUBMISSION REQUIREMENTS

Format for submission shall follow the CTD format detailed below:

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative information.

Summary of Product characteristics (SmPC) for a similar biotherapeutic product should be provided on 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.

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.

Other information on SmPC should be consistent with the RBP's SmPC. Any difference in the proposed SmPC vis-à-vis the RBP's SmPC, should be appropriately discussed and justified.

This section should follow the NDA guideline on SmPC (Guideline on submission of documentation for marketing authorization of pharmaceuticals for human use Doc No. PAR/GDL/004).

MODULE 2: OVERVIEW AND SUMMARIES

The purpose of this module is to summarize the quality (chemical, pharmaceutical, and biological), non-clinical and clinical information presented in modules 3, 4, and 5 in the market authorization application. The submission for this section will be as stipulated in the NDA guidelines for registration of biotherapeutics.

MODULE 3: QUALITY

The information requested under this section should be supplied in format stipulated in the NDA guidelines for 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 side-by-side physicochemical 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 shall be provided to support the application for registration. These batches may be pilot or production batches. If they are pilot batches, they shall 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 NDA guidelines for Applications for Registration of Biotherapeutics. 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 ingredient should 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, NDA Guidelines for Applications for Registrations of Biotherapeutics, ICH guidelines Q5A, Q5B and Q5D should be referred to.

Complete description of the manufacturing process including in-process controls should be provided. This should include 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:-

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

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

3.2.3 Characterization tests, process controls, and specifications that will emerge from information gained during process development shall 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.

3.2.4 The full Drug Master File (DMF), manufacturing process validation protocol and report should be submitted.

3.2.5 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 NDA guidelines for registration of Biotherapeutics.

3.3 Analytical Comparability

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 shall be provided.

Characterizations of a biological product by appropriate techniques, as described in **ICH Q6B** 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.

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 NDA 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 be 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.

MODULE 4: NON-CLINICAL STUDY

The establishment of safety and efficacy of a biosimilar usually requires the generation of some non-clinical data with the biosimilar. The spectrum of studies required to established safety and efficacy of the biosimilar 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. Non-clinical 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 non-clinical 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 NDA guideline for application of Registration for Biotherapeutics and ICH S6, should also be taken into account.

Additional non-clinical 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 NDA guideline for Registration of Biotherapeutics.

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

a) Quality-related factors:
b) Significant differences in the cell expression system compared with the RBP;
c) Significant differences in purification methods used;
d) 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.

e) Factors related to pharmaco-toxicological properties of the drug substance:

f) Mechanism(s) of drug action are unknown or poorly understood;

g) The drug substance is associated with significant toxicity and/or has a narrow therapeutic index;

h) 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. This 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 non-clinical part of the dossier.

b) If feasible, biological activity may be evaluated as part of the non-clinical 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 shall 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 biosimilar**.** 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 non-clinical 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.

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 shall 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 an 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 from the WHO guidelines on evaluation of similar biotherapeutic products.

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

5.3 Clinical Efficacy Trials

Comparative clinical trials (head-to-head adequately powered, randomised, 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 shall 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 biosimilar 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. 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 biosimilar 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 is insufficient to identify all these differences in safety. Therefore, applicant should submit a risk management plan/pharmacovigilance plan for the SBPs. The plan shall 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**.

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.

NDA recommends that immunogenicity assays be developed and validated with respect to both the proposed SBPs and RBPs 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 lasted 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.

5.6 Pharmacovigilance

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 pharmacovigilance plan/risk management plan at the time of submission of the marketing authorization application and a commitment to provide a Periodic Safety Update Report (PSUR) and a Period Benefit Risk Evaluation Report (PBRER) post registration. The principles of pharmacovigilance planning can be found in relevant guidelines such as **ICH E2E** while guidelines on the PSUR can be found on the NDA website

6.0 REFERENCES

EMA-Product-specific bioequivalence Guidance
https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/product-specific-bioequivalence-guidance

Guidance for Industry Q1A (R2) – Stability Testing of New Drug Substances and Products
https://www.fda.gov/media/71707/download

Guidance on similar medicinal products containing recombinant Granulocyte Colony Stimulating factor (G-CSF)
https://www.ema.europa.eu/en/documents/scientific-guideline/annex-guideline-similar-biological-medicinal-products-containing-biotechnology-derived-proteins_en.pdf

Guideline for non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues
https://www.ema.europa.eu/en/documents/scientific-guideline/first-draft-guideline-non-clinical-clinical-development-similar-biological-medicinal-products_en.pdf

Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-1.pdf

Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparinshttps://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-

non-clinical-clinical-development-similar-biological-medicinal-products-containing_en.pdf

Guideline on similar biological medicinal products containing and products monoclonal antibodies – non clinical and clinical issues
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-monoclonal-antibodies-non-clinical_en.pdf

Guideline on similar biological medicinal products containing interferon beta
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-similar-biological-medicinal-products-containing-interferon-beta_en.pdf

Guidelines for non-clinical and clinical development of similar biological medicinal products containing recombinant alfa-containing medicinal products
https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-non-clinical-clinical-development-similar-biological-medicinal-products-containing_en-1.pdf

Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), TRS 977, Annex 2
http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/TRS_977_Annex_2.pdf?ua=1

ICH Guideline S6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals https://www.ema.europa.eu/en/documents/scientific-guideline/ich-s6r1-preclinical-safety-evaluation-biotechnology-derived-pharmaceuticals-step-5_en.pdf

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

ICH Harmonised Tripartite Guideline Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process Q5E
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5E/Step4/Q5E_Guideline.pdf

ICH Harmonised Tripartite Guideline Pharmacovigilance Planning E2E
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2E/Step4/E2E_Guideline.pdf

ICH Harmonised Tripartite Guideline Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products Q5C
https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q5C/Step4/Q5C_Guideline.pdf

ICH Harmonised Tripartite Guideline The extent of population exposure to assess clinical safety for drug intended for long term treatment for non-life threatening conditions E1

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1/Step4/E1_Guideline.pdf

ICH Harmonised Tripartite Guideline Validation of Analytical Procedures: Text and Methodology Q2 (R1)
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

ICH Topic Q5A R1 Quality of Biotechnological Product: Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-r1-viral-safety-evaluation-biotechnology-products-derived-cell-lines-human-animal-origin_en.pdf

ICH Topic Q5B Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-b-analysis-expression-construct-cell-lines-used-production-r-dna-derived-protein-products_en.pdf

ICH Topic Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
https://www.ema.europa.eu/en/documents/scientific-guideline/ich-q-5-d-derivation-characterisation-cell-substrates-used-production-biotechnological/biological-products-step-5_en.pdf

ICH Topic Q6B 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

Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product
http://www.msk.nclinnovations.org/medregulations/v1/html/Guidance/Guidance_Quality%20Consideration%20for%20Biosimilars.pdf

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (Guidance for Industry)
https://www.fda.gov/media/82647/download

WHO Guidelines on the Quality, Safety, and Efficacy of Biotherapeutic Products Prepared by Recombinant DNA Technology
https://www.who.int/biologicals/WHO_rDNA_2nd_public_consultation_28_June_2013.pdf

APPENDIX 1: Application for Registration of Similar Biotherapeutic Products (SBPs)

National Drug Authority
Plot No. 19 Rumee Towers, Lumumba Avenue,
P.O. Box 23096, Kampala, Uganda.
email: ndaug@nda.or.ug; website: www.nda.or.ug
Tel: +256-414-255665, +256-414-347391/2

Application for Registration of Similar Biotherapeutic Products (SBPs)

MODULE 1: ADMINISTRATIVE INFORMATION	
1. PARTICULARS OF THE PRODUCT	
1.1.	Type of the medicinal product application New Biosimilar 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: Email:	

1.6.	Name and address (physical and postal) of Local Technical Representative:
(Company) Name: Address: Country: Telephone: Email:	
1.7.	Pharmaceutical Dosage form and route of administration
Dosage form:	
Route(s) of administration (use current list of standard terms)	
1.8.	Packing/pack size:
1.9.	Visual description (Add as many rows as necessary)
1.10.	Proposed shelf life (in months):
1.11.	Proposed shelf life (after reconstitution or dilution):
1.12.	Proposed shelf life (after first opening container):
1.13.	Proposed storage conditions:
1.14.	Proposed storage conditions after first opening:
1.15.	Other sister medicinal products registered or applied for registration
1.16.	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):
1.17.	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):
1.18.	Pharmacotherapeutic group and ATC Code
1.19.	Pharmacotherapeutic group
1.20.	ATC Code: (Please use current ATC code)
1.21.	If no ATC code has been assigned, please indicate if an application for ATC code has been made: Yes ☐ No ☐ *(to select applicable box, double click on the box and select "checked")*
1.22.	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)
1.23.	Country of origin:
1.24.	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:	☐ Withdrawn (by applicant after authorization) Country:

Date of authorization (dd-mm-yyyy): Proprietary name: Authorization number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	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:

1.25.	List ICH countries and Observers where the product is approved.
1.26.	Name(s) and complete physical address(es) of the manufacturer(s)
1.27.	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: E-Mail:	
1.28.	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: E-Mail:	
1.29.	Name and address (physical and postal) of the person or company responsible for Pharmacovigilance
Name: Company name: Address: Country: Telephone: E-Mail:	
1.30.	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.
1.31.	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

Name of excipient(s)			

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):

1.32.	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:

E-Mail:

1.33.	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:

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

APPENDIX 2: Summary Information for Similar Biotherapeutic Product

National Drug Authority
Plot No. 19 Rumee Towers, Lumumba Avenue,
P.O. Box 23096, Kampala, Uganda.
email: ndaug@nda.or.ug; website: www.nda.or.ug
Tel: +256-414-255665, +256-414-347391/2

Doc. No.: PAR/FOM/330
Revision No.: 0
Effective Date: 14 Oct 2019

Summary Information for Similar Biotherapeutic Product

< Name of the biosimilar medicinal product >
< National Drug Authority); Date..... >

PART A - ADMINISTRATIVE INFORMATION			
Sr. No.	**To be completed By**	**1. Biosimilar Product Information**	
1.1.	Applicant	**Name of the Similar Biotherapeutic Product**	< Invented/Trade name >
1.2.	Applicant	**MAH**	Name and address
1.3.	Applicant	**Active ingredient manufacturing facilities and batch release site for the finished product** (if applicable)	< Name(s) and address(es) > < Confidential – Not Released >
1.4.	Applicant	**Name of the active ingredient(s)**	(INN/ Common name/ Local name/ BQ if applicable)
1.5.	Applicant	**Pharmaco-therapeutic group**	e.g. ATC code
1.6.	Applicant	**Substance category**	As described in International Nonproprietary Names (INN) for biological and biotechnological substances https://www.who.int/medicines/services/inn/BioRev2014.pdf
1.7.	Applicant	**Pharmaceutical form**	Standard Term
1.8.	Applicant	**Quantitative composition**	Strength

1.9.	Applicant	**Route of administration**	Route
1.10.	Applicant	**Packaging/material**	Primary container
1.11.	Applicant	**Package size(s)**	Presentations available
1.12.	Applicant	**Local legal basis**	Legislative Reference
1.13.	Applicant	**Local Similar Biotherapeutic Product guidelines**	Reference to applicable guidelines
1.14.	NDA	**Date of authorisation/licensing of Similar Biotherapeutic Product**	Approval date for biosimilar
1.15.	**To be completed By**	**2. Reference Biotherapeutic Product (RBP) Information**	
2.1.	Applicant	**Name of the RBP**	Trade name of reference biotherapeutic product
2.2.	Applicant	**Authorised indications for RBP**	Indications approved for reference biotherapeutic product in full or summary + English reference
2.3.	Applicant	**Quantitative Composition/ Pharmaceutical form/ Route of administration (of RBP)**	As detailed
2.4.	Applicant	**Authorisation (Licence) number (of RBP)**	Registration number(s) of the RBP
2.5.	Applicant	**Date of authorisation (of RBP)**	Approval date(s) for reference biotherapeutic product
2.6.	Applicant	**Authorisation (Licence) Holder (of RBP)**	Company name of licence holder

2.7.	Applicant	**Source of RBP (or other comparator) for comparability exercise**	Region(s) where reference biotherapeutic product has been acquired in order to perform biosimilarity exercise.

Sr. No.	**To be completed By**	**3. Summary of outcomes**	
3.1.	Applicant	**Comparability exercise to demonstrate similarity to RBP**	High level summary of data included in comparability exercise for biosimilarity.
3.2.	Applicant	**Indications applied for** (if different to RBP)	Summary of indications requested in biosimilar application
3.3.	NDA	**Authorised indications for Similar Biotherapeutic Products**	Indications approved following review – in full or if available in English on NDA website: provide summary and link.

Sr. No.	**To be completed by**	**Data required**
4.1.	Applicant	**Quality data. Composition of the biosimilar product(s)**
		Provide name of active substance and strength. Provide names (qualitative) of excipients used in formulation.
4.2.	Applicant	**Quality data. State-of-the-art methods**
		Include high level summary of physicochemical test methods and biological activity studies used for characterisation.
4.3.	NDA	**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?).
4.4.	Applicant	**Mechanism of action**

Sr. No.	To be completed by	Data required
		Describe mechanism of action relevant to indications applied for.
4.5.	Applicant	**Non-clinical data. *In vitro* studies**
		Specify dose used and length of the study.
4.6.	Applicant	**Non-clinical data. *In vivo* studies**
		Specify animal model(s), e.g. dose used and length of the study.
4.7.	NDA	**Non-clinical data assessment outcome**
		Provide high level summary review of non-clinical data and outcome (any differences? If yes, why it was not considered to affect efficacy or safety of the product?).
4.8.	NDA	**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
4.9.	Applicant	**Clinical data. PK studies**
		Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study.
4.10.	NDA	**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?).
4.11.	Applicant	**Clinical data. PD studies**
		Specify study number(s) and summary of design, population, objective and endpoint, dose used and length of the study.

Sr. No.	To be completed by	Data required	
4.12.	NDA	**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?).	
4.13.	Applicant	**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.	
4.14.	NDA	**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).	
4.15.	Applicant	**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 study (ies).	
4.16.	NDA	**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 <biosimilar product> was considered to be comparable to that in the RBP, using appropriately validated methods.	
4.17.	Applicant	**Additional information about the comparability exercise**	As appropriate, if not previously included.

Sr. No.	To be completed by	Data required
4.18.	Applicant	**Post-authorization measures**
		Is a risk management plan available? Which Q/ S/ E studies are included?
4.19.	NDA	**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.>
4.20.	Applicant	**Availability of additional relevant information in the local language/ link**
		As required /appropriate

PART C - REVIEWER CONCLUSIONS

To be completed by NDA
Conclusions on biosimilarity and approval
The reviewer should comment and conclude on the following:- <The data provided by the Applicant was in line with the local legislation and guidelines.> <The data provided by the Applicant was in line with the local legislation, guidelines and international guidelines.> Quality All major physicochemical characteristics and biological activities of <biosimilar product trade name > were comparable to those of the reference biotherapeutic product <trade name >. Non-clinical No major differences in non-clinical 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 poulation> provided robust evidence of therapeutic equivalence versus the reference biotherapeutic product <trade name >. Additional data was provided < in another indication> to support biosimilarity 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 >. 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.

DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
073 Sep 2019	0	PAR/GDL/017	Mutyaba Michael Romeo Etuko Daniel Kemigisha Agnes Grant Munkwase	First issue

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