GUIDELINES ON REGISTRATION[1] OF SIMILAR BIOTHERAPEUTIC PRODUCTS

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[1] *In line with the National Drug Policy and Authority Act, Cap. 206 and the National Drug Policy and Authority (Registration) Regulations, 2014, the terms* ***"Registration" and "Holder of a Certificate of Registration"*** *as used in these guidelines are synonymous with the universally accepted term* ***"Marketing Authorization"*** *and* ***"Marketing Authorization Holder"****.*

Citation

These guidelines shall be cited as the *"Professional Guidelines on Registration of Similar Biotherapeutic Products, Doc. No. PAR/GDL/017, Revision No.:1".*

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.:1, made this 15th day of February 2023, that take effect on 20th February 2023.

Signature

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PREFACE

The National Drug Authority (NDA) requires that all pharmaceutical 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 product) is considered as a new biological product developed to be similar in terms of quality, safety and efficacy to an already registered, well established, 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 any person who submits an application for registration to the Authority and may be a patent holder; licensed person; the manufacturer; or an agent authorized by the manufacturer or patent holder.

"Authorised 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.

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 product 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 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 products means they have similar (no better or no worse) efficacy and any observed differences are of no clinical relevance.

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

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

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

"Immunogenicity" means the ability of a substance to trigger an immune response or reaction (e.g. development of specific antibodies, T cell response, allergic or anaphylactic reaction).

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

"Innovator Product" means a 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.

"Pharmacovigilance" means the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug related problem.

"Pharmaceutical product" means any medicine intended for human use and a veterinary product administered to food-producing animals, presented in its finished dosage form or as a starting material for use in the dosage form.

"Product" means a drug or preparation for human or veterinary use or a vaccine or other immunological product.

"Protein" means any alpha amino acid polymer with a specific defined sequence that is greater than 40 amino acids 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, which align with current global regulation of SBPs. It is intended to guide applicants on the Chemistry, Manufacturing and Control (CMC) section of a registration application for a proposed SBP. The registration 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.

An application for registration of a product may be made by;

a) the patent holder;
b) a licensed person;
c) the manufacturer; or
d) an agent authorised by the manufacturer or patent holder.

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 product, subsequently referring to the respective dossier.

1.2 Objective

The objective of this guideline is to guide the applicants and assessors on what needs to be submitted to support the registration of similar biotherapeutic 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

Regulation 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 registration 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 (Professional Guidelines on Submission of Documentation for Registration of Pharmaceutical Products 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 registration application. The submission for this section will be as stipulated in the Professional Guidelines on Registration of Biotherapeutics.

MODULE 3: QUALITY

The information requested under this section should be supplied in format stipulated in the Professional Guidelines on Registration of Biotherapeutics as follows:

3.2.S. Drug substance

The information requested under this section should be supplied individually for each active substance used in the final rDNA derived biotherapeutic product.

3.2.S.1 General information

3.2.S.1.1 Nomenclature

Information concerning the nomenclature of the active substance (e.g. proposed INN name, Pharmacopeial name, proprietary name, company/laboratory code (could include trade mark name), other names or codes, if any) and identification number of production strain should be provided.

Where an International Non-proprietary Name (INN) is available for rDNA-derived biotherapeutic, the INN should be used. The proper name should be the equivalent of the INN in the language of the country of origin.

A list of any inactive substances, which may be present in the bulk active substance, should be provided.

3.2.S.1.2 Structure

The structural formula, molecular formula and molecular weight should be provided as well as the schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass, as appropriate.

3.2.S.1.3 General properties

A list of physicochemical and other relevant properties of the active substance, including biological activity should be provided. The description of an rDNA-derived biotherapeutics should indicate the biological system in which it is produced (e.g. bacterial, fungal or mammalian cells) as well as the presentation of the drug product. Refer to ICH Topic Q6B for more details

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

The name, physical address and responsibility of each manufacturer, including contractors, and each production site or facility involved in the manufacturing and testing should be provided. The physical address should include units and blocks for each production site.

The sites or facilities involved in creation, testing and storing of the cell banks should be listed.

3.2.S.2.2 Description of manufacturing process and process controls

Information on the manufacturing process should be presented in the form of a flow diagram which indicates each step of the process including identification of the critical steps and points at which process controls are conducted.

A narrative description of the manufacturing process including information on cell bank and cell culture, harvest(s), purification and modification reaction including filling storage and shipping conditions should be provided. The in-process controls for each step or stage of the process should be indicated. Explanation should be provided on batch numbering system and any pooling of harvest or intermediates as well as scale of culture and batch

a) Cell culture

The following information should be provided:

i. Flow diagram from working cell bank (WCB) through harvest;
ii. Information for each stage should be provided (population doublings, cell concentrations, volumes, pH, cultivation time, temperature) and transfers between steps.
iii. Description of each step including any media, materials or additives used for both cell growth and for induction;
iv. Information with respect to operating parameters for each stage with links to section 3.2.S.2.4 (in-process controls) or specifications. Detailed information with respect to Production at infinite passage, continuous culture production and control of host-cell/vector characteristics at the end of production cycles for rDNA derived biotherapeutics can be referenced in ICH Topic Q5D, ICH Topic Q5B and WHO TRS 987

b) Purification

The following information should be provided:

i. Flow diagram from crude harvest, extraction and purification to final step of obtaining final active substance;
ii. Information for each stage should be provided (pH, conductivity, processing times, hold times, elution profiles, fraction (selection) including viral inactivation step(s);
iii. In-process controls, including acceptance criteria, should be described in detail and should be validated. Special attention should be given to the removal of viruses, nucleic acid, host cell proteins and impurities considered to pose a risk of immunogenicity;
iv. Particular attention should be given to demonstrating the removal and/or inactivation of possible contaminating viruses and residual DNA from products manufactured using continuous cell lines;
v. Description of each step including scale (columns, membranes), lifetime usage for resins/membranes, regeneration, buffers used, and transfer between steps;
vi. Reprocessing steps should be described with criteria.

Further guidance on control of residual cellular DNA from continuous cell line (rDNA) and virus clearance can be obtained from WHO TRS 987 and ICH topic Q5A

c) Drug substance filling, storage and transport
The following information should be provided:

i. Procedure used to fill active substance into container with associated process controls and acceptance criteria;
ii. Container closure system, storage and shipping conditions;
iii. Free/thaw or re-filtration procedures;
iv. Hold times should be specified.

3.2.S.2.3 Control of materials

Information on raw materials used in cell culture and purification should be described with respect to raw material grade or specification, product contact filter, media composition, resins and contact membranes.

Control of source and starting materials of biological origin (viral safety information) should be summarized and detailed information should be provided in 3.2.A.2.

a) Source, history and generation of cell substrate
A description of the host cell, its source and history, and of the expression vector used in production, including source and history, should be provided in detail. The description should include details of the origin and identity of the gene being cloned as well as the construction, genetic elements contained and structure of the expression vector. An explanation of the source and function of the component parts of the vector, such as the origins of replication, promoters, or antibiotic markers, should be provided in addition to a restriction-enzyme map indicating at least those sites used in construction.

Further information on cell substrate source, analysis of expression construct used to genetically modify cells and incorporate in the initial cell clone for Master cell bank can be obtained in the ICH topic Q5A; ICH topic Q5B; ICH topic Q5C; ICH topic Q5D and WHO TRS 987 guidelines.

b) Cell Banking system, characterisation and testing
Information on the cell banking system; quality control activities and cell line stability during production and storage (including procedures used to generate the Master and Working Cell Bank(s) should be provided in detail.

Information should include MCB and WCB, future WCB and End of Production Cell Bank and establishment of limit of in vitro cell age (LIVCA).

The type of cell bank system used, the size of the cell bank(s), the container (vials, ampoules, or other appropriate vessels) and closure system used, the methods for preparation of the cell bank(s) including the cryoprotectants and media used, and the

conditions employed for cryopreservation or long-term storage should all be documented and described in detail.

For animal cells and animal derived cell banks, reference should be made to WHO TRS 978, Annex 4.

3.2.S.2.4 Control of Critical Steps and Intermediates

Testing and acceptance criteria for the control of critical steps in the manufacturing processes should be provided.

Stability/Micro data to support hold times of process intermediates should be provided. Supportive data to be presented in section 3.2.S.2.5

Further requirement can be obtained in ICH Q6B

3.2.S.2.5 Process Validation and/or evaluation

a) Validation summaries of each unit operation, hold times, sanitary processing, and virus validation

Sufficient information on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiated selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g. cell culture, harvesting, purification, and modification) should be provided. Virus validation will also need to be discussed in 3.2.A.2.

b) Outline Validation strategy and scale used to complete studies

Information should include a description of the plan for conducting the study and the results, analysis and conclusions from the executed study (ies).

c) Reference analytical procedures used for analysis

The validation of corresponding assay and analytical methods should be cross-referenced or provided as part of justifying the selection of critical process controls and limits. For manufacturing steps, intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided

Validation process should include for example: Facilities, cleaning and microbiological control, Cell growth and harvesting e.g. Cell growth kinetics and antibody productivity profiles demonstrated for each bioreactor for appropriate timeframe, removal of media components/additives during purification and capacity of purification process to remove contaminating virus.

For more information, refer to EMA guideline on process validation for the manufacture of biotechnology-derived active substances and data to be provided in the regulatory submission.

3.2.S.2.6 Manufacturing Process Development

a) Development program outline, scale(s) and tools used (design of experiment, FMECA, statistical evaluations)

The developmental history of the manufacturing process, as described in section 3.2.S.2.2, should be provided.

b) Process description and batch information from development scale(s)

i. Outline any changes through development scale up to commercial (clinical batches)

The description of change(s) made to the manufacture of drug substance batches used in support of the registration application (e.g. non-clinical or clinical studies) including for example, changes to the process or critical equipment. The reason for the change should be explained. Relevant information on drug substance batches manufactured during development, such as the batch number, manufacturing scale and use (e.g. stability, non-clinical reference material) in relation to the change should also be provided.

ii. Major changes need to be assessed for potential impact on product quality

The significance of changes should be assessed by evaluating their potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance should be provided along with a discussion of the data including a justification for selection of the test and assessment of results.

iii. Selection of tests and results used to assess manufacturing changes during development

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding finished drug product(s) may also include non-clinical and clinical studies in other modules of the submission should be included.

iv. Process Characterisation shall include:

Establishment of operating parameters and in process controls for commercial scale manufacture.

Elimination of operating parameters/in process controls based on development work that deemed them non-critical.

Freeze/thaw development data used to set number of cycles for drug

substance.

Post approval – Comparability assessment of current to proposed change including side-by-side batch release data, Co-mixture analysis with reference standard and subset of initial characterisation testing to evaluation primary, secondary and tertiary structure.

It is recommended that information on study design and product knowledge should be presented in this section.

Refer to ICH topic Q5E and ICH topic Q11

3.2.S.3.1 Elucidation of Structure and other characteristics

Details on primary, secondary and higher order structure of product and product related substances, post-translational forms – glycoforms information on biological activity, purity and immunochemical properties (where relevant) should be provided.

3.2.S.3.2 Impurities

Information should be provided on both process and product related impurities with links back to section 3.2.S.2.2 and 3.2.S.2.4 for detailed information on removal and control of the respective impurities. There should be an investigation of impurities (e.g. aggregates including dimers and higher multiples of the desired product).

3.2.S.4. Control of active Substance

3.2.S.4.1 Specification

At minimum release specifications for drug substance shall include appearance and description, identity, purity and potency. Information on the source, including as appropriate species of animal, type of microorganism should be included in the specifications, etc.

For initial applications, acceptance criteria shall be based on data from pre-clinical/clinical, development, consistency of the lots and stability data as appropriate. Any specification changes post approval should take into consideration clinical experience when tightening specifications.

Further requirements can be obtained in ICH topic Q6B and WHO TRS 987, particularly Appendix 2

3.2.S.4.2 Analytical Procedures

The analytical procedure used for testing the active substance should be provided in sufficient detail to enable reproducible testing by another laboratory.

Analytical procedure summaries should be provided that minimally includes the following subsections: Principle**,** Procedure and Data Analysis.

3.2.S.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedure used for testing the drug substance should be provided. Typical validation

characteristics to be considered are selectivity, precision (repeatability, intermediate precision and reproducibility), accuracy, linearity, range, limit of quantitation, limit of detection, robustness, and system suitability.

Analytical method validation data should be performed to provide assurance of the method transferability to an additional testing site post initial approval.

3.2.S.4.4 Batch Analysis

Description of batches and results of three batch analyses should be provided. Results should be presented for three commercial batches against acceptance criteria. Consideration should include graphs and/or gels for those tests that are qualitative or where specification is “comparable to reference material".

3.2.S.4.5 Justification of Specification

Justification for the active substance specification should be provided.

Rationale for use of tests for specific quality attributes taking into account the specifications and linking to manufacturing process, stability of active substance, pre-clinical/clinical studies and analytical procedures should be provided.

3.2.S.5 Reference Standard

Quality information of Reference standard or material used for testing of active substance should be provided. The information should include a description of manufacturing process of reference standard, and where appropriate Characterisation, stability and storage of the reference standard should also be detailed.

Refer to ICH topic Q6B guidelines for details of acceptability of reference standards.

3.2.S.6 Container Closure system

A description of the container closure systems for the drug substance should be provided, including specifications for their component materials. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Suitability and compatibility of the materials of construct with active substance should also be demonstrated, literature reference may suffice when applicable.

3.2.S.7 Stability

Stability studies should include: Storage conditions i.e temperature and relative humidity for accelerated and stress conditions.

Stability studies should be done in accordance or with reference to WHO TRS 987, ICH Q1A and ICH Q5C guidelines.

3.2 Drug Product

This section should contain information on the final drug product including all drug substances and excipients. If any proprietary preparation or mixtures are used as components, a complete statement of composition and other information that will

properly describe and identify these materials should be provided.

For all ingredients of human or animal origin, testing results or certificates of analysis demonstrating freedom from adventious agents should be provided as in section 3.2.A.2.

3.2.P.1. Description and composition of drug Product

A description of the finished biotherapeutic product and its composition should be provided. The information provided should include:

a) Description of the dosage form;
b) Composition, i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any, the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications)
c) Description of accompanying reconstitution diluents (s) if any;
d) Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable
e) Overages need to be justified – not intended to compensate for inadequate stability or manufacturing process.

Tables provided under section 2.3.P.1. of the Quality Overall Summary (QOS) should be used to summarize the information for this part.

3.2.P.2. Pharmaceutical development

Information and data on the development studies conducted to establish the dosage form, the formulation manufacturing process, container closure system, microbiological attributes and usage instructions as appropriate for the purpose specified in the application, should be presented. Additionally, this section should identify and describe the formulation and process attributes (clinical parameters) that may influence batch reproducibility, product performance and drug product quality.

Manufacturing process changes made during clinical study programme should be explained and justified. A link between formulation development and clinical batches should also be provided.

Supportive data and results from specific studies or published literature may be included within or attached to the pharmaceutical development section. Additional supportive data may be referenced to the relevant non-clinical sections of the application. The report should include the following:

3.2.P.2.1 Drug Substance

The description and properties of the active substance should be provided. Compatibility with the rest of the components in the finished biotherapeutic product, including preservatives and other additives should be demonstrated, where applicable.

3.2.P.2.2 Drug Product

Information on the development of the formulation, considering the proposed route of administration should be provided. Details on the physicochemical and biological properties of the product, indicating the relevant parameters for developing the drug product should be included. In addition, justification of final qualitative/quantitative formula of the drug product should be provided.

3.2.P.2.3 Development of the manufacturing process

Description of the selection and optimization of the manufacturing process, particularly for critical aspects should be provided.

3.2.P.2.4 Container closure system selected

Information on the materials selected, protection against humidity and light, compatibility of the materials should be provided.

Information on the suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed. Results of extractable study should be presented and depending on the results, also a leachable study with e.g. placebo in final container should be presented.

3.2.P.2.5 Microbiological Attributes

Information on the integrity of the container closure system to prevent microbial contamination should be presented.

3.2.P.2.6 Compatibility

Information on the compatibility of the drug product with the manufacturing process contacts (e.g. online filters, bags), container closure system including dosage devices where applicable and diluents should be provided.

3.2.P.3 Manufacture processes of the drug product

6.2.P.3.1 Manufacturer

Name(s), physical address(es) including unit(s) and/or block(s) and functions of each manufacturing site involved in all stages of the processes should be listed.

Valid manufacturing licence and/or certificates of GMP compliance of the sites and other pertinent organizational information for each manufacturer responsible for any portion of the manufacture or testing operations for the Biotherapeutic products should be provided.

3.2.P.3.2 Batch formula

Batch lot formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages and a reference to their quality standards.

3.2.P.3.3 Description of the manufacturing process

A flow diagram should be presented giving the steps of the process, indicating the points where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative of the manufacturing process, equipment and materials used, the room or area where the operation is performed (may reference the simple floor diagram), in-process controls, and the critical points identified should be provided.

3.2.P.3.4 Control of critical and intermediate steps

Tests and acceptance criteria developed to identify the critical steps in the manufacturing process should be provided with justification. A listing of the in-process controls and tests performed on the product at each step should be submitted. Specifications for intermediate products should be provided and they should be followed during routine production.

3.2.P.3.5 Validation and/or evaluation of the processes

Description, documentation, and results of the studies on validation and/or evaluation of the manufacturing process, should be provided for the critical steps or critical tests employed in the manufacturing process. It is also necessary to provide information on the viral safety of the product, when applicable.

A product quality review may be submitted in lieu of the information below.

The following information should be provided:

a) A copy of the process validation protocol, specific to the biotherapeutic, that identifies the critical equipment and process parameters that can affect the quality of the product and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;
b) A commitment that three consecutive, production-scale batches of the biotherapeutic will be subjected to prospective validation in accordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification.
c) Validation information relating to the adequacy and efficacy of any sterilization process (e.g. product, packaging component should be submitted.

The process validation report should include inter alia the following:

i. A reference to the current master production document;
ii. A discussion of the critical equipment;
iii. The process parameters that can affect the quality of the biotherapeutic, critical process parameters (CPPs) including challenge experiments and failure mode operation;
iv. Details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender/ storage bins for uniformity testing of the final blend);

v. The testing parameters / acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;
vi. The analytical procedures or a reference to appropriate section(s) of the dossier;
vii. The results/data obtained.

Refer to EMA guideline on Guideline on process validation for finished products - information and data to be provided in regulatory submissions for more information.

3.2.P.3.6 Description of the batch identification system

Information on how the lots are defined in the stage of filling, lyophilisation (if it applies) and packaging should be provided.

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

Information on the specifications for all the excipients employed in the formulation should be provided.

List of raw materials meeting in-house specifications including the tests performed and specifications of biological starting materials (human or animal origin) with information on the requirements to avoid risk of transmissible spongiform encephlopathies (TSEs) and human diseases (HIV, hepatitis, etc) in the final product including Certificate of Suitability (CEP) should be included. The information should be provided as appendices to module III. (3.2.A)

3.2.P.4.2 Analytical procedures

Description or bibliographic reference of the analytical methods used to control all the excipients employed in the formulation should be submitted.

3.2.P.4.3 Validation of the analytical procedures

All analytical methods used to control the excipients in the final formulation should be validated and validation reports provided if applicable.

3.2.P.4.4 Justification of specifications

Justification for the proposed specifications of the excipients should be provided.

3.2.P.4.5 Substances of Human or Animal Origin

For excipients of human or animal origin, information should be provided regarding the source/origin, description of the quality tests performed, specifications, determination of adventitious agents and viral safety.

Additionally, testing results or certificates of analysis demonstrating their freedom from adventitious agents should be provided.

3.2.P.4.6 Novel excipients

When used for the first time in a recombinant DNA derived formulated biotherapeutic product for human use or for a new route of administration, detailed information should be provided on the manufacture, characterization, and control, and data supporting safety established in nonclinical and clinical studies in relation to the drug substance used.

3.2.P.5 Control of the finished biotherapeutic product

3.2.P.5.1 Specifications of the finished drug product

Specifications for the drug product should be provided. At minimum, specification should contain test and acceptance criteria for description and appearance, identity, quantity, potency, purity and impurities;

For Intermediate Products (as appropriate): Highlight the list of the routine tests performed and specifications for intermediates.

3.2.P.5.2. Analytical procedures of the drug product

Detailed information on the analytical procedures used for quality control of the drug product should be provided. This section should not be presented as summaries or references.

3.2.P.5.3. Validation of the analytical procedures;

Information on the validation of the analytical procedures for the drug product, including experimental data should be provided. This information should include complete description of the protocol used for each bioassay, the control standards, the validation of inherent variability of test and the establishment of acceptance limits for each assay.

3.2.P.5.4. Batch analysis

A description of all batches selected to assure the identity, purity, strength and/or potency, as well as the lot-to-lot consistency of the drug product and the specifications used for the drug product should be submitted.

Description should include (size, origin and use) and test result of all relevant batches e.g pre-clinical, clinical pilot, scale-up, and if available production-scale batches) used to establish specification and evaluate consistency in manufacturing.

Provide certificates of analysis and analytical results for at least three consecutive batches signed by authorized personnel

3.2.P.5.5 Characterization and/or determination of impurities

Details on the characterization and/or determination of impurities, as applicable, depending on the nature of active substance and method used to manufacture the biotherapeutic product should be provided.

3.2.P.5.6 Justification of specifications

Justification of the proposed biotherapeutic product specifications should be provided.

3.2.P.6 Reference standards and materials

Information on the reference standards and/or materials used for testing of the finished biotherapeutic product should be provided.

3.2.P.7 Container Closure System

Detailed description of the container closure system used for the drug product plus any accessories accompanied with it should be provided. The description should include the type and form of container closure system, including the materials of which they are made and quality specifications.

Detailed information concerning the supplier(s), address(es), and the results of compatibility, toxicity and biological tests should be included.

When a delivery device is presented as part of the drug product (e.g. prefilled syringe, single-use autoinjector), it is important to demonstrate the functionality of such a combination, such as the reproducibility and accuracy of the dispensed dose under testing conditions which should simulate the use of the drug product as closely as possibleFor multi-use containers such as vials or cartridges for a pen injector, proper in-use stability studies should be performed to evaluate the impact of the in-use period of the vial or the assembled device on the formulation and the functionality of the pen injector. Dose accuracy should be demonstrated for the first and last dose delivered. In addition, the effect of multiple injections/withdrawals on the closure system should be demonstrated.

Description should also be used on the specialized devices used to monitor consistency of delivery if they are intended to become an important part of the product's container closure system.

3.2.P.8 Stability of the Drug Product

3.2.P.8.1 Protocols and results of the stability study that justify the proposed validity period.

Stability study report including the study protocol, specifications, analytical methods, detailed description of the container closure system for the product evaluated, storage conditions (temperature and relative humidity) and results for at least three lots of drug product prepared from different lots of drug substances should be provided and the reports should contain conclusions as well as proposed validity period.

A minimum of twelve months' data at the time of submission should be provided in cases where storage periods greater than six months are requested, unless otherwise justified. For storage periods of less than six months, the stability data should cover the whole proposed shelf life. The stability studies should be submitted in controlled documentation.
Stability studies under accelerated and stress conditions, including the impact of the container closure system, should also be provided.

Refer to ICH topic Q5C, WHO TRS 953 Annex 2 and WHO TRS 962 Annex 3.

For drug products that require reconstitution, in use stability studies should be provided.

3.2.P.8.2 Post-approval stability program

Include the stability program or stability commitment to be carried out once the drug product is on the market, including the number of batches to be included in the study each year and the tests to be performed. These results should be submitted periodically to update the information on the stability of the drug product.

3.2.P.8.3 Stability data

Evidence should be provided to demonstrate that the product is stable for the proposed validity period under the indicated storage conditions.

The stability of each dosage form should be separately documented.

The summary results, which support the proposed expiration-dating period, under recommended conditions, in the final container and closure system, should be provided.

Stability data submitted should be for at least three consecutive batches and include the following:

a) Information on stability of drug product, quality control methods and rationale for the choice of tests for determining stability.

b) Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production.

For lyophilized products the data supporting the shelf-life of the product following reconstitution should be included.

If the drug product is frozen, data supporting the stability of the product through a stated number of freeze-thaw cycles should be provided.
A plan for an on-going stability program should be provided. This should include the protocol to be used, number of final lots to be entered into the stability protocol each year and how such lots will be selected. A stability study protocol should be provided.

The policy for assigning the date of manufacture of each component as well as the final product (e.g. combination formulation) and diluents, as appropriate should be described.

3.2.P.8.4 Shipping

Details should be provided on the measures used to guarantee adequacy of temperature and humidity conditions for shipping the drug product from the place of production to the place of final sale, including all the storage and distribution stages and indicating the controls performed in each of the stages. Declaration should be signed by quality control personnel.

3.2.A Literatures References

3.2.A.1 Appendices

3.2.A.2 Adventitious Agents Safety Evaluation

Information on control or avoidance of non-viral adventitious agents (TSE, bacteria, mycoplasma) should be supported by TSE certificates of suitability and ensure Raw material and/or production process controls in place

Viral Adventitious Agents

Viral safety evaluation studies to demonstrate that materials are safe and approaches use to test, evaluate and/or eliminate are suitable. This shall include

a) Materials of Biological Origin – cell bank testing
b) Production testing.
c) Viral testing of unprocessed bulk.
d) Viral Clearance studies – small scale demonstration of viral inactivation and removal steps used in manufacturing

3.2.A.3 Qualitative and Quantitative Particulars

Qualitative and Quantitative Particulars of SBP shall be presented in a tabular form as indicated in the Professional Guidelines 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.A.4 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.

3.2.A.5 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.

3.2.R Executed batch manufacturing record

Provide key literatures reference used, if applicable.

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.

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 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 registration. 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-registration 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 registration 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: +256-417788100	Doc. No.: PAR/FOM/329 Revision No.: 1 Effective Date: 20 Feb 2023 Page 1 of 7
Application for Registration of Similar Biotherapeutic Products (SBPs)		

MODULE 1: ADMINISTRATIVE INFORMATION	
1. PARTICULARS OF THE PRODUCT	
1.1.	Type of the product application New Biosimilar Renewal* * If variation has been made, information supporting the changes should be submitted. See variation guidelines for registered 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 products registered or applied for registration
1.16.	Do you hold Marketing Authorization (s) of other 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 of 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 Product from National Medicines Regulatory Authority). If not registered, state reasons

☐ Authorized Country: Date of authorization (dd-mm-yyyy):	☐ Withdrawn (by applicant after authorization) Country: Date of withdrawal (dd-mm-yyyy):

Proprietary name: Authorization number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	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 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: +256-417788100

Doc. No.: PAR/FOM/330
Revision No.: 1
Effective Date: 20 Feb 2023

Summary Information for Similar Biotherapeutic Product

< Name of the biosimilar 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

PART A - ADMINISTRATIVE INFORMATION			
Sr. No.	**To be completed By**	**1. Biosimilar Product Information**	
1.13.	Applicant	**Local Similar Biotherapeutic Product guidelines**	Reference to applicable guidelines
1.14.	NDA	**Date of registration of Similar Biotherapeutic Product**	Approval date for biosimilar
2.0	**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	**Registered 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** 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. a) Pharmacokinetic, PK b) Pharmacodynamic, PD c) Efficacy d) Safety e) 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.
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?).

Sr. No.	To be completed by	Data required
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.
4.18.	Applicant	**Post-registration measures**
		Is a risk management plan available? Which Q/S/E studies are included?
4.19.	NDA	**Post-registration 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.> <u>Quality</u> All major physicochemical characteristics and biological activities of <biosimilar product trade name > were comparable to those of the reference biotherapeutic product <trade name >. <u>Non-clinical</u> No major differences in non-clinical data were observed for <biosimilar product trade name > compared to the reference biotherapeutic product <trade name >. <u>Clinical Studies</u> The PK / PD / efficacy studies to demonstrate biosimilarity conducted in < patient poulation> provided robust evidence of therapeutic equivalence versus the reference biotherapeutic product <trade name >. Additional data 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 >. <u>Risk Management</u> < The risk management plan (or equivalent) was considered to be acceptable. > < No additional risk management activities are foreseen post-approval.> <u>Overall Conclusion</u> <Satisfactory assurance of biosimilarity was demonstrated using an appropriate comparability exercise> <Concerns raised during the review relating to < summarise major issues > were resolved during the procedure.> The biosimilar product <trade name > was considered approvable.

DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and reasons for revision
07 Oct. 2019	0	PAR/GDL/017	Mutyaba Michael Etuko Daniel Kemigisha Agnes	First Issue
15 Feb. 2023	1	PAR/GDL/017	Mutyaba Michael Romeo Etuko Daniel Kemigisha Agnes Grant Munkwase	i. Changed from Marketing Authorization to Registration; and marketing authorization holder to Holder of a Certificate of Registration wherever applicable ii. Added description for product and pharmaceutical product iii. Revised medicinal product to pharmaceutical product in compliance with the NDP&A Act and Regulations iv. Added more information on module 3 Quality (Added the chemistry, manufacturing an d quality control sections for the active substance and finished product.

End of Document