GUIDELINES FOR REGISTRATION OF BIOSIMILAR PRODUCTS

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018. One of the functions of Rwanda FDA is to regulate matters related to quality, safety and efficacy of Similar products in order to protect public health by increasing their access and availability.

Considering the provisions of the technical regulation N° DFAR/HMDAR/TRG/001 governing the registration of pharmaceutical products which gives the power to issue the guidelines, the Authority issues *Guidelines DFAR/HMDAR/GDL/003 for registration of Biosimilar products.*

The Authority adopted the Common Technical Document (CTD) Guidelines for registration of Biosimilar Products in Common Technical Document (CTD) format. However, due to nature of biosimilar product, some Common Technical Document (CTD) sections described in the Guidelines for the Registration of Biological Products are not applicable.

These guidelines are intended to provide guidance on issues to consider when demonstrating that a proposed biological product is similar to, a reference biological product already registered and well established for purposes of submitting a marketing authorization application. These guidelines apply to well-established and well-characterized biological products such as recombinant DNA-derived therapeutic proteins.

The Authority acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines.

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Director General

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Rev 1	1) Adoption of the new Guidelines template 2) Adoption of the new document number format 3) Change of the title to make it clear and concise 4) Change of mode of application submission 5) Update of the registration certificate content and format 6) Update of the application processing timeline 7) Update of the application requirements 8) Editorial changes

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ABBREVIATIONS AND ACRONYMS

BMRs	Batch Manufacturing Records
BMWP	Biologicals Monitoring Working Party
CA	Clinical Assessor
CHMP	Committee for Medicinal Products for Human Use
CMC	Chemistry, Manufacturing and Controls
DNA/ rDNA	Deoxyribonucleic Acid/Recombinant DNA
EAC	East African Community
EMA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Council for Harmonization
INN	International Non-proprietary Names
MOA	Mechanism of Action
NCE	New Chemical Entity
NMRA	National Medicines Regulatory Authority
PBRER	Periodic Benefit-Risk Evaluation Report
Ph. Eur	European Pharmacopeia
PK/PD	Pharmacokinetic/Pharmacodynamic
RBP	Reference Biological Product
RMP	Risk Management Plan
Rwanda FDA	Rwanda Food and Drugs Authority
biosimilar product	Similar Biological Product
WHO	World Health Organization

DEFINITIONS

The definitions provided below apply to the words and phrases used in these guidelines. The following definitions are provided to facilitate interpretation of the guidelines. Other terminologies can be found in the Rwanda FDA common glossary of terms.

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

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

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

"**Applicant"** means a person who applies for registration of a human medicinal pharmaceutical product to Rwanda FDA, who must be the owner of the product. He may be a manufacturer or a person to whose order and specifications, the product is manufactured. After the product is registered, the applicant shall be the Marketing Authorization Holder.

"**Local Technical Representative (LTR)"** means any registered company in Rwanda and licensed by Rwanda FDA to deal with regulated products that has received a mandate from the Applicant to act on his/her behalf with regard to matters pertaining to the registration of regulated products.

"**Manufacture"** means all operations that involve preparation, processing, filling transforming, packaging, and repackaging and labelling of medicinal products.

"**Manufacturer"** is a person or firm that is engaged in the manufacture of Similar Biological Products. It involves operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

Manufacturing process means the transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

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

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

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

"Cell bank" means a facility that stores cells of specific genome for the purpose of future use in a product or medicinal needs.

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

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

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

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

"**Biological products**" means 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.

"Biosimilar products" means a product that is similar to a biological product that has been already been authorised. This product 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 biosimilar product are based on the demonstration of similarity (i.e. no clinically meaningful difference between the biosimilar product and the reference biological product) in terms of quality, safety and efficacy to an already registered, reference biological product.

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

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

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

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

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

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

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

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

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

"Non-clinical (Pre-clinical)" means during pre- clinical drug development, a sponsor evaluates the drug's toxic and pharmacologic effects through in vitro and in vivo laboratory animal testing. Generally, genotoxicity screening is performed, as well as investigations on drug absorption and metabolism, the toxicity of the drug's metabolites, and the speed with which the drug and its metabolites are excreted from the body.

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

"Pharmacovigilance" means, the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problems. The decision to approve a drug is based on a satisfactory balance of benefits and risks within the conditions specified in the product labeling. This decision is based on the information available at the time

of approval. The knowledge related to the safety profile of the product can change over time through expanded use in terms of patient populations and the number of patients exposed. In particular, during the early post-marketing period the product might be used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use.

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

"Reference Biological Product": a reference **Biological** product is used as the comparator for head-to-head comparability studies with the Biosimilar 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" 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.

"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 Rwanda. A variation also includes, but is not limited to, a change in the product name, site of manufacture and/or source of ingredients.

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

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

1. INTRODUCTION

1.0 Background

Rwanda Food and Drugs Authority (Rwanda FDA) is established by the Law N° 003/2018 of 09/02/2018, especially in its article 8 and 9;

Considering the provisions of the technical regulation governing the registration of human medicinal products, the Authority has issued Guidelines for registration of Biosimilar products.

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

Biological 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 Biosimilar Products is appropriate. For these reasons, the standard generic approach is scientifically not applicable to development of biosimilar product and additional non-clinical and clinical data are usually required. Immunogenicity of biosimilar products is of concern from clinical and safety perspective. Clinical trials and a robust post-market surveillance/pharmacovigilance plan are essential to guarantee that the product is safe and efficacious over time.

These guidelines were developed to describe the regulatory framework for biosimilar productss in Rwanda, which align with current global regulation of biosimilar products. It is intended to guide applicants on the Chemistry, Manufacturing and Control (CMC) section of a marketing application for a proposed biosimilar product. The marketing application must include

information demonstrating biosimilarity, based on data derived from, among other things, analytical studies that demonstrate that the biological is highly similar to the RBP notwithstanding minor differences in clinically inactive components.

Although the regulatory framework applies generally to biological products, this guidance document focuses on biosimilar product 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.

Biosimilar products 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 biological product and the reference biological product should be justified by appropriate studies.

References:

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

1.1 The concept of Biosimilar products

The concept of a biosimilar Product applies to biological drug submission in which the manufacture would be based on demonstrated similarity to a Reference Biological Product (RBP).

The rationale for creating the new regulatory framework to evaluate biosimilar product is that biological 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 biosimilar product. The large and complex molecular structure of biologics makes them difficult to adequately characterize in the laboratory.

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 biological product' in terms of quality, safety and efficacy to one chosen reference medicinal product, subsequently referring to the respective dossier.

1.2. Scope

These guidelines apply to well-characterized and established molecules, their derivatives and products of which they are components, and which are isolated from microorganisms, tissues, body fluids, cell cultures, or produced using rDNA technology. Thus, the document covers the generation and submission of efficacy, potency, stability and toxicological data for biological 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 and blood products, heparins, and in-vitro diagnostics.

2. GENERAL INFORMATION

2.1 General Requirements

For general requirements of application for registration of biosimilar products reference should be made to the Authority's guidelines on submission of documentation for registration of Biosimilar Products, available at the Authority's website by dully filling an application form in annex I *(Refer to the Annex-II*)

Biosimilar product submission must follow the format described in the authority's Guidelines for the Registration of biosimilar products. Due to nature of biosimilar product, some sections described in the Guidelines for the Registration of biosimilar products are not applicable.

2.2 Consideration for the Choice of Reference Biological Product

The aim of the biosimilar approach is to demonstrate close similarity of the biosimilar product in terms of quality, safety and efficacy to a Reference Biological Products (RBP).

The following criteria should be considered in selecting RBP;

a. The RBP should have been marketed for an appropriate duration and have a volume of marketed use such that the demonstration of similarity to it, brings into substantial body acceptable data regarding the safety and efficacy.
b. The manufacturer must demonstrate that the chosen RBP is suitable to support the application for marketing authorization of biosimilar product.
c. The RBP should have been licensed on the basis of full quality, safety, and efficacy data. A biosimilar product should therefore *not* be chosen as an RBP.
d. The same RBP should be used throughout the development of the biosimilar product (i.e. throughout the comparative quality, nonclinical, and clinical studies).
e. The active ingredient of the RBP and the biosimilar product must be shown to be similar.

f. The dosage form and route of administration of the biosimilar product should be the same as that of the RBP.

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

1. The RBP should be licensed and widely marketed in another jurisdiction that has a well-established regulatory framework and principles, as well as considerable experience of evaluation of biological products and post-marketing surveillance activities.
2. The acceptance of an RBP for evaluation of a biosimilar product does not imply that the Authority has approved the RBP for use.

2.3. Product specific requirements

It should be recognized that there may be subtle differences between biosimilar products 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 biosimilar products given to patient should be clearly labeled and identified (by the brand name) by the prescriber.

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

a) Analytical assessment (physicochemical and functional studies) demonstrating the biosimilar 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 biosimilar product.

d) Risk management/pharmacovigilance plans

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

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

2.4.2. Expert report

Experts must provide detailed reports of the documents and particulars, which constitute sections 3, 4 and 5 for module 1, module 2 and module 3 respectively.

The requirement for these signed Expert Reports may be met by providing:

i. The Quality Overall Summary, Non-clinical Overview/Summary and Clinical Overview/Summary
ii. A declaration signed by the experts
iii. Brief information on the educational background, training and occupational experience of the experts

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

2.5. Scientific Guidelines applicable to all biosimilar products

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

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

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

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

The submission must follow Common Technical Document (CTD)s format detailed in Rwanda FDA Guidelines for the Registration of Biosimilar Products. Followings are requirements specific to biosimilar product dossiers that are submitted for registration:

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative information as stipulated in Guidelines for the Registration of Biosimilar products.

The applicant shall prepare and present the product dossier information in Common Technical Document (CTD) format with respect to the following requirements:

The application must contain a complete index to the various appendices. An application for biosimilar product registration in Rwanda shall include the following:

1. Signed and dated original copy of cover letter (Annexe 1)
2. Signed and dated application form for product registration (Annexe 2)
3. Payment of registration fee in accordance with regulations governing tariff/fees and charges on services rendered by Rwanda Food and Drug Authority. The fees are for each respective product registration excluding transfer and other charges
4. CTD document Format in (PDF), QOS in MS-Word

The applicant shall prepare and present the product dossier information in CTD format according to the requirements as stipulated in these guidelines:

a) The application should be typed in English, French or Kinyarwanda. Any document which is in any language other than English, French or Kinyarwanda must be accompanied by a certified or notarized translation.
b) The application must contain a complete index to the various appendices.
c) The summaries (Quality Overall Summary) should be formatted as word document as per templates downloadable on Authority's website.
d) All other documents shall be selectable and searchable.
e) All pages of the application should be numbered in the style: page x of y.
f) Two commercial samples of each pack size with respective Certificates of Analysis (CoAs).
g) Rwanda FDA GMP certificates or Proof of GMP inspection application to Rwanda FDA

Summary of Product characteristics (SmPC) for a similar biological product should be provided in A4 size and real size copies (on a CD/DVD-ROM or external driver in MS-Word of the package insert that contains a Summary of Product Characteristics (SmPC) aimed at medical practitioners and other health professionals using the format outlined below.

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

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

This section should follow the Rwanda FDA guidance on SmPC

MODULE 2: OVERVIEW AND SUMMARIES

The purpose of this module is to summarize the quality (chemical, pharmaceutical, and biological), nonclinical and clinical information presented in modules III, IV, and V in the market authorization application. The submission for this section will be as stipulated Guidelines for the Registration of Biosimilar products.

MODULE 3: QUALITY

The information requested under this section should be supplied in format stipulated in Rwanda FDA Guideline for the Registration of Biosimilar products.

The quality part of a biosimilar product, like all other biological products should comply with established scientific and regulatory standards. Biosimilar product manufacturer should provide full information on Chemistry, manufacturing and control.

In addition, the biosimilar product manufacturer is required to submit extensive data focused on the similarity, including comprehensive comparative (head-to-head) physicochemical, molecular and biological characterization (these may include bioassays, biological assays, binding assays, and enzyme kinetics) of the biosimilar product and the RBP.

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

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

3.1 Qualitative and Quantitative Particulars

Qualitative and Quantitative Particulars of biosimilar product shall be presented in a tabular form as indicated in Rwanda FDA Guidelines for the Registration of Biological products.

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

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

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

3.2 Manufacturing process

The manufacturing process for biosimilar product should be highly consistent and robust. The process should be developed and optimized taking into account state-of-the-art technology in relation to the manufacturing processes and consequences on product characteristics.

For the establishment and characterization of the cell banks, Rwanda FDA Guidelines for the Registration of Biological products, ICH guidelines Q5A, Q5B and Q5D should be referred to.

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

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

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

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

c) Characterization tests, process controls, and specifications that will emerge from information gained during process development must be specific for the proposed biosimilar product and the manufacturing process. The use of Quality-by-Design approaches is recommended to assure consistent manufacturing of high-quality product.

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

e) Product employing clearly different approaches to manufacture from the reference product will not be eligible for registration as a biosimilar product. The applicant shall be required to provide information to fulfill the requirements for registration of new biological products as prescribed in the Rwanda FDA Guidelines for the Registration of Biological products.

Reference

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

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

iii. **ICH Q5D:** *Derivation and Characterization of Cell Substrates used for Production of*

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

3.3 Analytical Comparability studies

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

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

3.4 Analytical procedure/technique/Product characterization

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

Extensive analytical methods should be applied to increase the likelihood of detecting subtle variations in the quality attributes of the product. Methods used in both the characterization studies and comparability studies should be appropriately qualified and validated [as in **ICH Q2** (**R1**)]

Reference standards and international reference materials shall be used for method qualification and validation. Specifications and Certificates of analysis for both reference standards and raw materials from the manufacturer must be provided by the applicant.

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

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

References

ICH Q2 (R1): Validation of Analytical Procedure: Test and Methodology. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q2_R1/Step4/Q2_R1__Guideline.pdf

ICH Q6B: *Note for guidance on specifications: Test Procedures and Acceptance Criteria for Biotechnological/ Biological products*. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002824.pdf

3.5 Container closure system

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

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

3.6 Product stability

The stability studies should comply with relevant *Rwanda FDA Guidelines for application of Registration for Biologicals (*DHT/GDL/013), ICH Q5C and Q1A (R2). Studies should be carried out to show that the biodegradation profiles are comparable between biosimilar product and RBP. Generally, stability studies results should be summarized in a tabular format, and they should include the results from real time and accelerated degradation studies and studies under various stress conditions (temperature, light, humidity and mechanical agitation).

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

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

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

References

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

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

MODULE 4: NON CLINICAL STUDY

The establishment of safety and efficacy of a biosimilar product usually requires the generation of some non-clinical data with the biosimilar product. The spectrum of studies required to established safety and efficacy of the biosimilar product 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 Rwanda FDA and/or any other 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 biosimilar product and the RBP.

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

4.1 Special consideration

The design of an appropriate nonclinical study should consider the product characteristics. Results from the physicochemical and biological characterization studies should be reviewed from the point of view of potential impact on efficacy and safety. In the development of biosimilar product, existing guidelines such as *Rwanda FDA Guidelines for the Registration of Biological products (DAR/GDL/00)* and ICH S6, should also be taken into account.

Reference

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm074957.pdf

Additional nonclinical data may be required to establish the safety and efficacy of biosimilar product depending on the product and on factors related to substance class as stipulated in the *Rwanda FDA Guidelines for the Registration of Biological* products

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

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

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

Depending on these factors, the spectrum of studies required to establish the safety and efficacy of the biosimilar product 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 biosimilar product 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:

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

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

4.3 Toxicology

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

a) Determination and characterization of antibody responses, including anti-product antibody titres
b) Cross-reactivity with homologous endogenous proteins, and
c) Product-neutralizing capacity.

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

A head-to-head repeat dose toxicity study should usually constitute a minimum requirement for non-clinical evaluation of a biosimilar product. Comparative repeat-dose toxicity studies should be submitted to demonstrate that no “unexpected” toxicity will occur during clinical use of the biosimilar product. 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 biosimilar product 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 biosimilar product and RBP by the additional comparability exercise performed as part of the quality evaluation, other routine toxicological studies – such as safety pharmacology, reproductive toxicology, genotoxicity and carcinogenicity studies – are not generally requirements for the nonclinical testing of an biosimilar product, 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.

References:

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

MODULE 5: CLINICAL STUDY

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

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

Clinical programmes for a biosimilar products 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 Rwanda FDA and/or competent authority should be present in the submission.

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

Further guidance on statistical considerations and extrapolations of indications can be obtained in WHO guidelines on evaluation of Similar biological product.

5.1 Pharmacokinetic (PK) studies

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

a) If appropriate from an ethical point of view, healthy volunteers will in most cases represent a sufficiently sensitive and homologous model for such comparative PK studies.

b) Choice of designs must be justified and should consider factors such as clearance and terminal half-life, linearity of PK parameters, where applicable, the endogenous level and diurnal variations of the product under study, production of neutralizing antibodies, conditions and diseases to be treated.

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

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

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 biosimilar products and the RBPs should be compared in a population where the possible differences can be best observed.

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

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

Reference

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

5.3 Clinical efficacy trials

Comparative clinical trials (head-to-head adequately powered, randomized, parallel group clinical trials, so-called ‘equivalence trials”) are required to demonstrate the similarity in the efficacy and the safety profiles between the biosimilar products and the RBPs. Assay sensitivity must be ensured (refer to **ICH E10**).

Equivalence margins should be pre-specified and adequately justified on clinical grounds. Equivalent rather than non-inferior efficacy should be shown in order for the biosimilar products 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 product to the reference product and therefore need to employ testing strategies that are sensitive enough to detect relevant differences between the products, if present.

5.4 Clinical safety and effectiveness

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

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

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

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

Reference:

ICH E1: *The extent of population exposure to assess clinical safety for drug intended for long-term treatment for non-life threatening conditions.*

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

5.5 Clinical Immunogenicity

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

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

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

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

The proposed biosimilar products and RBPs should be evaluated in the same clinical trial of sufficient duration with the same patient sera whenever possible. The duration of the study should be at least **12 months** using appropriate route of administration by comparative parallel designs. At the time of submission, the study should have covered at least **6 months**.

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

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

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

Reference is to be made to the CHMP Guidelines 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 biosimilar products; this should be done by prescriber.

Reference:

EMA guidelines

- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietins (EMA/CHMP/BMWP/3016636/2008).*
- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing recombinant human insulin and insulin analogues (EMA/134217/2012).*
- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing recombinant Granulocyte Colony Stimulating factor (rG-CSF) (EMEA/CHMP/BMWP/31329/2005).*
- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins (EMEA/134870/2012).*

- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing recombinant alfa-containing medicinal products (EMEA/CHMP/BMWP/102046/2006).*
- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing recombinant beta-containing interferon beta-containing medicinal products (EMEA/CHMP/BMWP/652000/2010).*
- *Guidelines for non-clinical and clinical development of similar biological medicinal products containing monoclonal antibodies- (EMEA/CHMP/BMWP/403543/2010).*

5.6 Pharmacovigilance

As for most biological medicines, data from pre-authorization clinical studies are usually too limited to identify all potential unwanted effects of an biosimilar product. In particular, adverse events are unlikely to be encountered in the limited clinical trial populations being tested with the biosimilar product. Further close monitoring of the clinical safety of an biosimilar product in all approved indications and a continued benefit-risk assessment are therefore necessary in the post-marketing phase.

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

Reference:

ICH E2E (Pharmacovigilance Planning)

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

REFERENCES

1. World Health Organization (WHO) Guidelines on Evaluation of Similar Biological Products (biosimilar product), 2013 WHO Guidelines on the Quality, Safety, and
2. Efficacy of biological protein products prepared by recombinant DNA technology, June 2013
3. ICH Guidelines.
4. EMA guidelines: (EMA-Product-specific biosimilar guidelines)
5. FDA-Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
6. FDA-Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

ENDORSEMENT OF THE GUIDELINES

	Prepared by	**Checked by**		**Approved by**
Title	**Division manager**	**Head of Department**	**Quality Assurance Analyst**	**Director General**
Names				
Signature				
Date				

ANNEXES

ANNEX I: COVER LETTER

< Applicant>
< Address>
<Postal Code>
< Town>
<Country>
<Date>

<Rwanda FDA>
<P.O.BOX 1948> <Kigali>
< Rwanda >

Dear Sir/Madam,

Subject: Submission of Application Dossier(s) for Marketing Authorization of <Product Name(s), [strength(s)] of active ingredient(s) and dosage form(s)

We are pleased to submit our Application Dossier(s) for a registration of biological product that details are as follows:

Name of the biological product(s): ……

Pharmaceutical form(s) and strength(s): ……..

INN/active ingredient(s): …….....

ATC Code (s): ……

You will find enclosed the submission dossier as specified hereafter:

☐ CTD format documents

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☐

☐ The electronic submission contains the following modules:

Module 1: Administrative information and product information

Module 2: Overview and summaries

Module 3: Quality (CMC)

Module 4: Nonclinical study reports

Module 5: Clinical study reports

I confirm that the Product Dossier information submitted including composition, formulation, strength, specifications and packaging is the same in all aspects as the product registered with the relevant SRA, WHO PQ and EAC (Only for Abridged Application)
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

Yours sincerely,

<Signature>

<Name>

<Title>

<Phone number(s)>

<Email address>

ANNEX II: APPLICATION FORM FOR REGISTRATION OF BIOSIMILAR PRODUCTS

1. For Rwanda FDA use only (highlighted portion).

Application Number	Rwanda FDA use only
Date of submission of the dossier	Rwanda FDA use only

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

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

☐Authorized Country: Date of authorization (dd-mm-yyyy): Proprietary name: Authorization number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	☐ Withdrawn (by applicant after authorization) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: ☐ Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name:
1.15	List ICH countries/Observers and EAC countries where the product is approved.

1.16	Name(s) and complete physical address(es) of the manufacturer(s)
1.16.1	Name(s) and physical address (es) of the manufacturing site of the drug product, including the final product release if different from the manufacturer. Alternative sites should be also declared here. All manufacturing sites involved in the manufacturing process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed. (Add as many rows as necessary)
Company name: Address: Country: Telephone: Skype: E-Mail: website:	
1.16.2	Name(s) and physical address(es) of the manufacturer(s) of the drug substance (Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites should be listed.
Company name: Address: Country: Telephone: Skype: E-Mail: website:	
1.17	Name and address (physical and postal) of the person or company responsible for Pharmacovigilance
Name: Company name: Address:	

Country: Telephone: Skype: E-Mail: website:	
1.18	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.
1.19	Qualitative and Quantitative composition of the drug substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g. 1 capsule).

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

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

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

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

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

1.21	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted
Company name: Address: Country: Telephone: Skype: E-Mail: Website:	
Name and address (physical and postal) of the site(s) where the non- clinical studies of the product were conducted	

Company name:
Address:
Country:
Telephone:
Skype:
E-Mail:
Website:

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 on the market and provide safety update reports to the Authority.

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

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

It is hereby confirmed that fees have been paid according to the regulation Nº CFO/TRG/004 and a proof of payment is hereby attached.

Name: ……..…….
Position in the company:……
Signature: ……..……
Date:……..
Official stamp:……..

Annex III: DECLARATION OF THE APPLICANT

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

a) The current edition of the **"***Rwanda FDA guidelines on Good Manufacturing Practices for finished pharmaceutical products*"
b) The formulation per dosage form correlates with the master formula and with the batch manufacturing record.
c) The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record.
d) Each batch of all starting materials is either tested or certified (in accompanying certificate of analysis for that batch) against the full specifications in the accompanying documentation and must comply fully with those specifications before it is released for manufacturing purposes.
e) All batches of the drug substance(s) are obtained from the source(s) specified in the accompanying documentation.
f) No batch of drug substance will be used unless a copy of the batch certificate established by the manufacturer is available.
g) Each batch of the container closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before released for the manufacturing purposes.
h) Each batch/lot of the biosimilar products is either tested, or certified (in an accompanying certificate of analysis for that batch), against the full specifications in the accompanying documentation and complies fully with release specifications before released for sale.

i) The person releasing the product is an authorized person as defined by **"***Rwanda FDA guidelines on Good Manufacturing Practices for finished pharmaceutical products*".

j) The procedures for control of the Drug product have been validated. The assay method has been validated for accuracy, precision, specificity and linearity.

k) All the documentation referred to in this application is available for review during GMP inspection.

l) Non-clinical and clinical data were conducted in accordance with Good Clinical Practice,

I also agree that:

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

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

Name:

Qualification:

Position in the company:

Signature & Official Stamp:

Date: