RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR REGISTRATION OF HUMAN BIOLOGICAL PRODUCTS

FEBRUARY, 2024

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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 Biological Products in order to protect public health from falsified and substandard Biological Products.

In consideration of the provisions of the technical regulations N° DFAR/HMDAR/TRG/001 governing the registration of pharmaceutical products which recommends issuing guidelines, the NRA issues *Guidelines N° DD/HMDR/GDL/006 for the registration of Human Biological Products.*

These guidelines have been developed based on the scientific quality, efficacy, and safety requirements adopted from WHO TRS 987(Annex 4) and EAC guidelines on submission for documentation for registration of biotherapeutic products and domesticated to have consistent and harmonized guidance.

They have been developed to guide the applicants and the Authority in managing applications for registration of Biological Products using the Common Technical Document format as they prepare the product dossier for submission of documentation for registration of Biological products.

These guidelines apply to well-established and well-characterized Biological Products in vitro diagnostic antigens, immunoglobulin, antisera, antitoxins, vaccines, and toxoids.

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

Digitally signed by Rwanda FDA (Director General)
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Director General

DOCUMENT DEVELOPMENT HISTORY

First issue date	25/01/2021
Effective date of this revision	29/02/2024

DOCUMENT REVISION HISTORY

Revision number	Changes made and/or reasons for revision
Rev 0	1) First Issue
Rev 1	1) Adoption of the new Guidelines template 2) Adoption of the new document number format 3) Change of mode of application submission 4) Update of the registration certificate content and format 5) Update on submission requirements 6) Update on timelines for product registration 7) 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
EMEA	Europe, the Middle East and Africa
EU	European Union
EPC	End of Production Cells
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
MCB	Master Cell Bank
NCE	New Chemical Entity
NMRA	National Medicines Regulatory Authority
NRA	National Regulatory Authority
PBRER	Periodic Benefit-Risk Evaluation Report
Ph. Eur	European Pharmacopeia
PK/PD	Pharmacokinetic/Pharmacodynamics
RBP	Reference Biotherapeutic Product
RMP	Risk Management Plan
Rwanda FDA	Rwanda Food and Drugs Authority
SBP	Similar Biotherapeutic Product
US FDA	United States Food and Drugs Administration
WHO	World Health Organization

DEFINITIONS

The definitions provided below apply to the words and phrases used in these guidelines. They are provided to facilitate interpretation of the guidelines. Other technical terms are found in the Rwanda FDA glossary of terms (Refer to the Guidance No DFAR/HMDAR/GDC/008). In these Guidelines, unless the context otherwise states:

***"API"* (Active Pharmaceutical Ingredient)** means any substance or mixture of substances intended to be used in the manufacture of a drug product by formulation with excipients and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body.

*"**Applicant"*** means a person who applies for registration of a human 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 Authorisation Holder.

"Antibody" means a spectrum of proteins of the immunoglobulin family that are 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 can 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.

*"**Authority**"* means Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established under article 2 of Law No. 003/2018 of 09/02/2018.

"Batch" 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.

"Batch" also means "a **lot**".

"Biologicals" includes in vitro diagnostic antigens, immunoglobulin, antisera, antitoxins, vaccines, and toxoids.

i. ***Antisera*** are preparations of antibodies of animal origin intended to treat or provide immediate protection against infections.

ii. ***Diagnostic antigen*** is a crude or purified fraction isolated from microbial culture and intended for in vitro detection of an existing specific immune response, usually by intradermal or percutaneous skin testing.

iii. ***Immunoglobulins*** are preparations of antibodies of human origin intended to treat or provide immediate protection against infections.

iv. ***Vaccine*** is an immunogen, the administration of which is intended to stimulate the immune system to result in the prevention, amelioration, or therapy of any disease or infection.

A vaccine may be a live attenuated preparation of bacteria, viruses, or parasites, inactivated (killed) whole organisms, living irradiated cells, crude fractions or purified immunogens, including those derived from recombining DNA in a host cell, conjugates formed by covalent linkage of components, synthetic antigens, polynucleotides (such as the plasmid DNA vaccines), living vectored cells expressing specific heterologous immunogens or cells pulsed with the immunogen. It may also be a combination of immunogens as listed above.

"Biologics" means Biological Products, which include a wide range of products such as vaccines, blood and blood components, allergenic, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues. Biologics are isolated from a variety of natural sources - human, animal, or microorganism and may be produced by biotechnology methods and other cutting-edge technologies. They are often at the forefront of biomedical research and may be used to treat a variety of medical conditions for which no other treatments are available.

"Immunogenic Substance" An immunogenic substance is an unformulated active substance that may be subsequently formulated with excipients to produce a pharmaceutical product. Immunogenic substances may be whole bacterial cells, viruses, or parasites (live or killed), crude or purified antigens isolated from killed or living cells; crude or purified antigens secreted from living cells, recombinant or synthetic carbohydrate, protein, or peptide antigens, polynucleotides (as in plasmid DNA vaccines) or conjugates

"ICH" **means International Conference on Harmonization 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 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, developing immunity, tolerance or hypersensitivity to the antigen.

"Immunogenicity" means the ability of a substance to trigger an immune response in a particular organism.

"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.

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

"Pharmaceutical product" means
Any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct, or carry out modification of organic or mental functions. It also means products used in disinfecting premises in which food and drugs are manufactured, prepared, or stored, cleaning hospitals, equipment, and farm houses.

"Local Technical Representative" means a 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 about the registration of regulated products.

"Marketing Authorization /registration certificate" means a legal document issued by the competent authority for the purposes of marketing or free distribution of a product that has been approved after evaluation for safety, efficacy, and quality;

"Marketing Authorisation Holder (MAH)" means a company that holds authorization to place a pharmaceutical product in the Rwandan market and is responsible for that product.

"Manufacturer" means a manufacturer is a natural or legal person with responsibility for the manufacturing of a pharmaceutical product or immunogenic substance.

"Master Cell Bank (MCB)" means an aliquot of a single pool of cells that generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers, and stored under defined conditions. The MCB is used to derive all working cell banks. The testing performed on a new MCB (from a previous initial cell clone, MCB or WCB) should be the same as for the MCB unless justified.

"Master Virus Seed (MVS)" means a viral seed of a selected vaccine virus from which all future vaccine production will be derived, either directly, or via Working Virus Seeds.

"Pharmacopoeias" Means a current edition of:

- British Pharmacopoeia, (B.P)

- European Pharmacopoeia, (Ph.Eur)
- International Pharmacopoeia, (IP)
- United States Pharmacopoeia, (USP)

"Pharmacovigilance" according to the WHO definition 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 labelling. 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.

"Pre-clinical (non-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.

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

"Product" means intermediates, drug substances, and /or drug products, as appropriate. The use of the term "product" is consistent with the use of the term in **ICH Q5E**.

"Reference Biotherapeutic Product" means a reference Biotherapeutic product used as the comparator for head-to-head comparability studies with a similar biotherapeutic product to show similarity in terms of quality, safety, and efficacy. It must contain an active biological substance with proven quality, safety and efficacy through non-clinical (toxicity) and clinical studies.

"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. 'Conformance to specification' means that the drug substance and drug product, when tested according to the listed analytical procedures, will meet the acceptance criteria. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities as conditions of approval.

"Validation" means 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. In the manufacturing of pharmaceutical products, production processes, cleaning procedures, analytical methods, in-process control test procedures, and computerized systems all have to be validated.

INTRODUCTION

1.1 Background

These guidelines have been developed based on the scientific guidelines and recommendations for quality, efficacy, and safety adopted from WHO TRS 987, Annex 4, and East African Community (EAC) Guidelines on submission of documentation for registration of Biotherapeutic products. Some aspects of manufacturing and quality control in these guidelines may apply to Biological Products such as vaccines, blood and blood components, allergenic, somatic cells, cellular and gene therapy products, tissues, and recombinant therapeutic proteins. Additional considerations for similar Biotherapeutic products have been addressed in the Guidelines for registration of Similar Biotherapeutic Products. Guidance on various aspects of Biological Products is also available from several other bodies such as the International Council on Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), the European Medicines Agency (EMA), and the United States Food and Drugs Administration (US-FDA).

The requirements for registration of Biological Products shall be by the Common Technical Dossier (CTD) format as described in sections of these guidelines. The guidelines describe the format in which dossiers should be presented in support of the application for registration of Biological product. According to the CTD format, each application is a collection of documents, grouped into 5 modules. Module 1 prescribes Administrative Information and Prescribing Information requirements, which is region specific. The Overviews and Summaries, Quality, Non-clinical, and Clinical modules have been described in Modules 2 to 5. These guidelines, therefore, contain the following sections:

Module 1: Administrative and Product Information
Module 2: Overview and Summaries
Module 3: Quality (Chemistry, manufacture and controls)
Module 4: Non-clinical study reports
Module 5: Clinical study reports
Appendix I: Cover letter template
Appendix II: Application form
Appendix III: Expert Declaration form
Appendix IV: Quality Overall Summary
Appendix V: Marketing Authorisation / Registration Certificate for Biological Product

Information in these modules should be presented in relevant sections. Any additional data including experts' comments should be included as an addendum to the relevant part and may be provided as a supplement to, and/or incorporated into the relevant summary.

1.2 Scope

These Guidelines apply to Biological Products such as vaccines, blood and blood components, allergenic, somatic cells, cellular and gene therapy products, tissues, and recombinant therapeutic proteins to guide applicants on the content and format of the Chemistry, manufacturing, and controls (CMC) data of such products required for their complete scientific evaluation. They also indicate the order of documents to be submitted and all the requirements for registration.
They should be used in conjunction with other national and international guidance documents available from the Rwanda FDA, WHO, EMEA, ICH, and the US FDA that describe the CMC, non-clinical, and clinical requirements appropriate for evaluating Biological Products.

Adherence to these guidelines by applicants will facilitate the timely review and processing of product registration.

1.3 Application requirements

An application for Biological product registration in Rwanda shall include the following:

1. Signed and dated original copy of a 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.

5. Two commercial samples of each pack size with respective Certificates of Analysis (CoAs);
6. Rwanda FDA GMP certificates or Proof of GMP inspection application to Rwanda FDA.

1.4 Submission of application

An application for Biological product registration for either locally manufactured or imported shall be made in writing *via* a cover letter and application form dated and signed by the applicant. If the applicant is a foreign company, the applicant shall appoint a local technical representative through whom an application shall be submitted.

The application shall be submitted through the Rwanda FDA online Portal (https://www.irims.rwandafda.gov.rw/portal/). A reference number is automatically assigned to the application and it will be used in all subsequent correspondences relating to the application. An acknowledged receipt will be issued automatically by the system. Two commercial samples of each pack size shall be submitted to Rwanda FDA Head Office. Those samples should be accompanied by a cover letter (annex-1) and a printed notification email clearly stating the application reference number generated by the Rwanda FDA portal at the time of submission.

1.5 Officially Recognized References

The officially recognized pharmacopeias by the Authority are British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.), The International Pharmacopoeia (Ph.Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP). References should be cited under the current edition of compendia.

1.6 Harmonization with other international regulators

Rwanda FDA harmonizes its registration processes as much as possible with other competent, Stringent Regulatory Authorities (SRAs) and international organizations such as the World Health Organization (WHO) and the International Conference on Harmonization (ICH).

Where specific guidelines are unavailable, Rwanda FDA adopts Committee for Medical Product for Human Use (CHMP) Guidelines, which are available at the following websites EMEA: http://www.emea.europa.eu and International Conference on Harmonization (ICH) Guidelines: http://www.ich.org.

1.7 Rwanda FDA Dossier Assessment Procedures

The application of product registration is received by the Authority through the system. After receiving the product application, the Rwanda FDA shall proceed with screening of the dossier for completeness. In the event that the dossier is incomplete, it will not be scheduled for assessment and the applicant will be notified within **30 calendar days** and requested to comply with requirements in writing.

In case of a positive outcome during the screening, the application will be scheduled for assessment according to the First in First out (FIFO) rules. Priority assessment may be granted where the product is intended for treatment of rare disease conditions (Reference to guidelines for registration of medical products for Unmet medical needs) or in the case of emergency situation (reference to guidelines of Emergency use).

Additionally, abridged assessment maybe conducted in case, the product is eligible for reliance procedure (Reference to the guidelines on reliance for regulatory decision making and guideline for abbreviated assessment).

A product dossier is reviewed by two assessors to provide scientific and regulatory oversight regarding the quality, safety and efficacy of the product under assessment.

Rwanda FDA reserves the right to request any additional information to establish the quality, safety and efficacy of a Biological Product in Rwanda. During the assessment, additional data and/or samples may be requested through the system. Once a query has been issued to the applicant, the assessment process stops until Rwanda FDA receives a response to the raised queries. Further processing of the application may only be undertaken if responses to issued queries contain all outstanding information requested in one submission. Failure to comply with this condition or if the queries have been reissued for a **third** time and the applicant provides unsatisfactory responses, the application will be rejected (**Figure 1**).

In the event that the responses to the queries are not submitted within specified timeline from the date they were issued, it will be considered that the applicant has withdrawn the application unless the applicant has requested for extension of the deadline to Rwanda FDA. Thereafter, registration of the product may only be considered upon submission of a new application.

1.8 Compliance to the current Good Manufacturing Practices (cGMP)

The GMP inspection is part of the product registration process. Rwanda FDA should inspect the facility or use other means to verify whether the manufacturing site complies with cGMP regulations and/or guidelines before a product is registered. No product shall be registered unless the facility complies with cGMP. During the assessment, assessors may highlight GMP issues and communicate to the division that has the mandate of inspection and compliance. More information on cGMP requirements and application for GMP inspection is detailed in the Rwanda FDA Guidelines on Good Manufacturing Practices and its annexes (*Refer to the GMP guidelines document and its annexes*) downloadable from the Rwanda FDA website.

1.9 Internal Scientific Review Committee for Product Registration

After the completion of the Dossier Assessment, a final assessment report shall be presented to the **Internal Technical Committee** for review and recommendation for marketing authorization approval or rejection.

In the event, that there are safety, quality, or efficacy issues to be resolved as per the decision of the committee, the application shall remain pending until the resolution of the raised issues. If the applicant fails to provide the required data within the specified timeline the application shall be considered as **withdrawn.**

Rwanda FDA will register the product if data on safety, quality, and efficacy is considered satisfactory and a registration certificate of Biological products (***Refer to the Appendix V-document)*** will be granted. The registration shall be valid for a period of five (**5**) years. If the

Rwanda FDA suspends or cancels the registration validity, a written official communication shall be made to the applicant.

1.10 Timelines for Product Registration

Product dossiers shall be scheduled for assessment according to the First in First out (FIFO) basis upon compliance with the requirements. A new application shall be processed within **twelve** (**12**) months of receipt of the application (Figure 1).

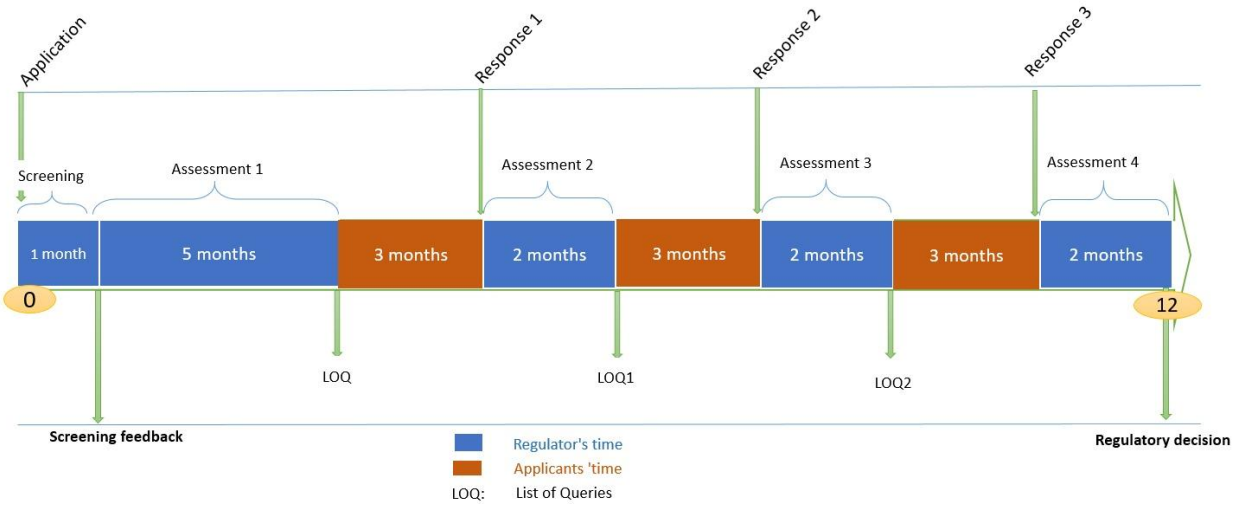

Figure 1. Graphical illustration of timelines

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative information as stipulated in Guidelines for the Registration of Biological Products (for example, application forms and certifications), labelling, general correspondence, and annexes.

A separate application is required for each product, i.e., products containing the same ingredients but made to a different specification (in terms of strength or content of active ingredients, dosage form, etc.) or by a different manufacturer.

However, products other than injectable, made by the same manufacturer to the same specifications, strength (content) of ingredients, and form, but differing only in packing or pack sizes require only one application.

Documents should be organized in the order listed below. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes.

1.1 Comprehensive table of contents

Module 1 should include a comprehensive table of contents for the entire application. The comprehensive table of contents should include a complete list of all documents provided in the application by module. In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document.

1.2 Cover Letter

Applicant should include a cover letter in all applications. A copy of the letter should be placed at the beginning of Module 1. The cover letter shall be dated and signed by the applicant (proposed Market Authorization Holder) (***Refer to appendix I-***).

1.3 Application form

An application to register a biological product must be accompanied by a completed Application Form (Appendix II). The application form should be dully filled with relevant information and attachments, dated signed and stamped appropriately.

1.4 Product Information

Provide copies of all package inserts, labels and any information intended for distribution with the product to the patient.

1.4.1 Summary of product characteristics (SmPC)

The SmPC is the basis of information for healthcare professionals on how to use biological products safely and effectively. A summary of the characteristics of the biological product under evaluation should be submitted.

If the Summary of Product Characteristics (SmPC), has not been approved from SRA at the time the application is submitted, a draft document may be included. The approved SmPC from SRA should then be submitted to the Authority as they become available.
The SmPC should be as described in Rwanda FDA *Guidance on format and content of Summary of Product Characteristics for pharmaceutical products.*

1.4.2 Container labeling

Products should be labeled as prescribed in the *Guidance on Format and Content of Labels for Pharmaceutical Products.*
In some circumstances, for specific Biological Products especially vaccines, the shelf life may not be indicated on the label. In this regard, the Authority follows the labeling requirement recommended by WHO or other recognized SRAs.

1.4.3 Package insert

All biological preparations with the exception of medicines for hospital use only shall contain a patient information leaflet as prescribed in the *Guidance on Format and Content of Patient Information Leaflets for Pharmaceutical Products.*

1.4.4 Mock-up and specimens

If the product applied for registration has a specimen or mock-up of the sample(s) presentation of the biological product available at the time of initial application should be included in section 1.5.4 of module 1.

The purpose of this is to provide an example of the product, including accessories, if any, to verify that they correspond to what is described for the characteristics of the product under evaluation. If there are multiple strengths and/or pack sizes, one representative specimen or mock-up for each will be sufficient. If the batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels.

If mock-ups or specimens are not available at the time of initial application, a text version may be submitted, however, mock-ups or specimens must be submitted to the Authority, during the evaluation process and before finalization of the application.

1.4.5 Information about experts

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

- The Quality Overall Summary, non-clinical Overview / Summary, and Clinical Overview / Summary in Module 2.
- A declaration signed by the experts in module 1.5.5.
- Brief information on the educational background, training, and occupational experience of the experts in Module 1.5.5.

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. An Expert declaration form is provided ***(Refer to Appendix III)***

1.5 Certificates of Suitability of monographs of the European Pharmacopoeia (CEP) or EAC-APIMF

If CEP is available, the applicant should present a copy of CEP in section 1.6.
The applicant should provide the Letter of Access to CEP or Letter of Access to APIMF, as appropriate from the API manufacturer. These letters should be included in Module 1.6.

1.6 Certificate of Good Manufacturing Practices (GMP)

A certificate of GMP compliance should be submitted. This should include manufacturers that are involved in any stage of the production process, for example, manufacturer(s) of the finished biological product, active substance(s), the diluents, and those responsible for labelling and packaging of the finished biological product. More information on GMP requirements and application for GMP inspection is detailed in the Rwanda FDA *Guidelines on Good Manufacturing Practices* and its annexes.

1.7 Good Clinical Practice (GCP) and/or Good Laboratory Practice (GLP)

Evidence such as accredited certificate for GCP or GLP for the sites participating in the clinical studies should be submitted.

1.8 Regulatory Status

1.8.1 Registration status within EAC and SRAs/WLAs)

The applicant should provide a list of ML3 countries having MoU with Rwanda FDA, countries in EAC, and countries with a WHO listed Authorities (WLAs)/ List of transitional WLAs in which a similar application has been submitted, dates of submission (if available) and the status of these applications. This should detail approvals (with indications) and deferrals, withdrawals, and rejections with reasons in each case.

1.8.2 Statement on whether an application for the product has been previously rejected, withdrawn, or repeatedly deferred

A declaration of whether a marketing application for the biological product has been rejected before submission of the application in Rwanda should be submitted. If the Biological product has been rejected, repeatedly deferred, withdrawn, or suspended then reasons should be stated.

1.9 Evidence of API and/or FPP prequalified by WHO or registered in the other stringent regulatory authorities

If evidence indicating that the drug substance and/or drug product have been prequalified by WHO is available, or if FPP is registered in the other stringent regulatory authorities, it should be presented under this section.

1.10 Manufacturing and Marketing Authorization

A Certificate of Pharmaceutical Products in the format recommended by the World Health Organization should be submitted together with a valid Manufacturing Authorization for pharmaceutical production. If available, evidence for prequalification of a Biological Product by WHO should also be submitted.

1.11 Product samples

Two commercial samples in the final packing size of each pack size with a certificate of analysis applied for marketing authorization should be submitted together with the application to enable visual inspection of the product and product package. However, additional samples may be requested depending on tests or parameters to be carried out.

1.12 Authorization of the Local Technical Representative

Any applicant for Biological Product Registration who is not resident in Rwanda shall appoint a local technical representative (LTR) who must be a company authorized by Rwanda FDA to deal in pharmaceutical products. The appointment shall be notified to the Authority by submitting a letter of appointment from the applicant supported by an original copy of power of attorney duly notarized in the country of origin authorizing the company to represent the manufacturer and market the product in Rwanda.

1.13 Environmental risk assessment

Evaluation of the possible environmental risks posed by the use and/or disposal of the Biological Product should be submitted. In addition, proposals in that regard and the indications or warnings to be included on the product label should as well be submitted.

1.14 Manufacturer's declaration

A document should be presented certifying that the information provided is the information corresponding to all the studies performed, regardless of their results. This should include all the pertinent information regarding all toxicological and/or clinical tests or trials of the Biological Product that are incomplete or have been abandoned and/or completed tests related to indications not covered by the application. The mentioned declaration from the manufacturer should be submitted in this section.

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 3, 4, and 5 in the market authorization application. The experts who draft these summaries should take an objective approach to the decisive points related to the quality of the product, and clinical and nonclinical studies performed, report all pertinent data for the evaluation, and refer to the corresponding tables included in modules 3, 4, and 5. The information in module 2 should be presented in world format in the following order:

2.1 General table of contents

A general index should be included of the scientific information contained in modules 2 to 5.

2.2 Introduction

A summary of the type of product, composition, mechanism of action, and indications proposed for the biological product.

2.3 Overall quality summary

A general summary of the quality of the product should be presented, related to the chemical, pharmaceutical, and biological aspects. This summary should refer exclusively to the information, data, and justifications included in module 3 or in other modules of the product dossier. This section should follow format as specified in the Quality Overall Summary format ***(Refer to Appendix IV).***

2.4 Overview of nonclinical studies

A comprehensive and critical assessment of the results of the evaluation of the biological product in animals and in vitro testing should be presented and the safety characteristics of the same for use in humans should be defined.

The Nonclinical Overview should be presented in the following sequence:

2.4.1 Overview of the nonclinical testing strategy
2.4.2 Overview of Pharmacology
2.4.3 Overview of Pharmacokinetics
2.4.4 Overview of Toxicology
2.4.5 Integrated overview and conclusions
2.4.6 List of literature references

2.5 Overview and summary of clinical studies

This section should include a critical analysis of the clinical study results included in the clinical summary and module 5. Information should include an overview and summary of the clinical development of the product, the design of the pivotal studies, and the decisions related to the clinical studies and their performance and it should include an overview of the clinical conclusions and an evaluation of the risks/benefits concerning the results of the clinical studies and justification of the proposed dosages. All the data related to efficacy/effectiveness and safety assessed through the development of the product should be summarized in this section and presented, as well as any study limitations. Summaries should include all the clinical studies performed and a synopsis of each study.

The data should be presented in a written and tabulated summary in the following order:

2.5.1 Introduction
2.5.2 Detailed discussion of the product development
2.5.3 Overview and summary of immunogenicity
2.5.4 Overview and summary of the efficacy
2.5.5 Overview and summary of the safety
2.5.6 Conclusions on risk/benefit analysis
2.5.7 Literature References

2.6 Non-clinical written and tabulated Summaries

A summary of the results of the pharmacological, pharmacokinetic, and toxicological tests on animals and/or “in vitro” should be included. An objective written and tabulated summary should be presented in the following order:

The data should be presented as a written and tabulated summary, in the following order:

2.6.1 Introduction
2.6.2 Written pharmacological summary
2.6.3 Tabulated pharmacological summary
2.6.4 Written pharmacokinetic summary (when appropriate)
2.6.5 Tabulated pharmacokinetic summary (when appropriate)
2.6.6 Written toxicological summary
2.6.7 Tabulated toxicological summary

In general, clinical overview and summaries should not exceed 50 pages.

MODULE 3: QUALITY (CHEMISTRY, MANUFACTURING AND CONTROLS)

This module is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products as defined ICH Guideline Q6B.

3.1 TABLE OF CONTENTS OF MODULE 3

In accordance with the general plan agreed internationally for registration of Biological Products.

3.2 CONTENTS

Corresponds to the basic principles and requirements of the active ingredient(s) and finished product. This includes the chemical, pharmaceutical, biological data on development, the manufacturing process, certificates of analysis, characterization and properties, quality control, specifications and stability of each of the active ingredients and finished product as indicated below.

3.2.S Active biological substance.

The information requested under this point should be supplied individually for each active substance where applicable.

3.2.S.1 General information, starting materials and raw materials

3.2.S.1.1 Nomenclature

Information on the nomenclature of the Active biological substance (e.g., proposed INN name, Pharmacopeia 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 an Active biological substance, 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, that may be present in the bulk active biological 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 active substance should indicate the biological system in which it is produced (e.g., bacterial, fungal or mammalian cells) as well as the presentation of the finished product. Refer to ICH Q6B.

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.
A valid manufacturing authorization should be provided for the production of all active substance(s). If available, a certificate of GMP compliance should be provided in the product dossier.

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 drug substance can be referenced in ICH Q5D, ICH Q5B and WHO TRS 987, Annex 4.

b) Purification

The following information should be provided:

i. Flow diagram from crude harvest, extraction and purification to final step to obtain 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 a continuous cell line (rDNA) and virus clearance can be obtained from WHO TRS 987, Annex 4; http://www.who.int/biologicals/biotherapeutics/TRS_987_Annex4.pdf?ua=1 and ICH 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 following guidance: ICH Q5A; ICH Q5B; ICH Q5C; ICH Q5D; WHO TSR 987, Annex 4.

b) Cell Banking system, characterization 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 3.

3.2.S.2.4 Control of Critical Steps and Intermediates

Testing and acceptance criteria (with justification including experimental data) 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 *Refer to 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 substantiate the 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.

It is expected that the manufacturing processes for all active substances are properly controlled. If a biological active substance is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the biological active substance during storage and transportation should also be provided Alternate processes should be justified and described.

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.

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 inactive viral contaminants, the information from evaluation studies should be provided

The 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 **(Refer to EMA/CHMP/BWP/187338/2014).**

3.2.S.2.6 Manufacturing Process Development

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

The developmental history of the manufacturing process, as described in 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 the change(s) made to the manufacture of drug substance batches used in support of the marketing 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) about the change should also be provided.

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

The significance of change should be assessed by evaluating its 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 substances 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 Characterization shall include:**

a) Establishment of operating parameters and in-process controls for commercial scale manufacture.
b) Elimination of operating parameters/in process controls based on development work that deemed them non-critical.
c) Freeze/thaw development data used to set number of cycles for drug substance.

d) 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 characterization 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 Q5E and ICH Q1).**

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of Structure and other characteristics

For the intended product and product-related substances, details should be provided, if applicable, on primary, secondary and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical/immunogenicity properties.

Rigorous characterization of biotherapeutic by chemical, physicochemical and biological methods is very relevant to be availed in the application dossier.

In terms of the primary structure, appropriate approaches are recommended such as peptide mapping and molecular weight determination by mass spectroscopy. According to glycan structure, the combined enzymatic or chemical hydrolytic cleavage with means of separation methods (High Performance Liquid Chromatography, Electrophoresis) and detection/identification methods (Mass Spectroscopy such as MS/MS, UV, fluorescence detection, electrochemical detection).

In terms of higher-order structure, characterization should be carried out by appropriate physicochemical methodologies and confirmed by biological function. It is recommended to avail data whereby appropriate analytical procedures were applied namely circular dichroism, FT-IR spectroscopy, fluorescence, differential scanning calorimetry, proton-NMR, and/or other suitable techniques such as hydrogen-deuterium exchange MS.

A summarized description of the intended product and product-related substances and a summary of general properties, characteristic features, and characterization data, such as primary and higher-order structure and biological activity, should also be provided.

<u>End of Production Cells (EPC)</u>

For r-DNA derive biological substances, a detailed description of the characterization of the EPC that demonstrates that the biological production system is consistent during growth shall be provided. The results of the analysis of the EPC for phenotypic or genotypic markers to confirm identity and purity shall be included. This section should also contain the results of test supporting the freedom of the EPC from contamination by adventitious agents.

The results of restriction enzyme analysis of the gene constructs in the EPC shall be submitted. Detailed information on the characterization and testing of banked cell substrates shall be submitted. This shall include the results of testing to confirm the identity, purity and suitability of the cell substrate for manufacturing use **(Reference ICH Guideline: Q6B).**

3.2.S.3.2 Impurities

Information on impurities should be provided. All potential impurities, including process related impurities and degradation products for purification arising from manufacturing, storage or found in stability study batches, should be described regardless of whether they have been detected in any batches.

The actual impurity levels detected (including quantities found in clinical, toxicological, bioavailability, and proposed commercial batches) should be reported, for example, using a summary table.

The information should also include a discussion of results which are close to or outside limits. A rationale should be provided for the choice of tests used, the proposed limits and their qualification.

A rationale for excluding any impurity test(s) from routine release testing due to trace levels should also be provided, where applicable.

3.2.S.4 Control of active Substance

3.2.S.4.1 Specification

At minimum release specifications for Active 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. **(Refer to *ICH Q6 B and* WHO TRS 987, Annex 4 - 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 to 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 the use of tests for specific quality attributes taking into account the specifications and linking to the manufacturing process, stability of active substance, pre-clinical/clinical studies, and analytical procedures should be provided.

3.2.S.5 Reference Standard

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

3.2.S.6 Container Closure system

A description of the container closure systems for the active 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 container closure system should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the active substance, including adsorption to container and leaching, and/or safety.

3.2.S.7 Stability

Stability studies should include: Storage conditions i.e., Temperature and relative humidity for accelerated and stress Conditions **(Refer to TRS WHO TRS 987, Annex 4, ICHQ1A and ICH Q5C).**

3.2.S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. Should include the study conditions, including all of the storage conditions (temperature, humidity, light) in which the drug substance is evaluated, analytical methods, specifications, summary of results, and conclusions.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

The post-approval stability protocol and stability commitment should be provided

3.2.S.7.3 Stability Data

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Genetic stability

- construct stability
- stability up to and beyond the maximum passage level used for full-scale production
- occurrence of the vector inside the cell (extra chromosomal or integrated)
- copy number
- amplification of gene construct

3.2.P Drug product

This section should contain information on the final drug product including all active 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 adventitious 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 biological 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

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 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 result 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 Active Substance

The description and properties of the active substance should be provided. Compatibility with the rest of the components in the finished biological 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 selection

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

3.2.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 license 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 drug 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 should be provided.

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.

- Batch and Scale Definition. An explanation of the batch numbering system and scale at each stage of manufacture (e.g., filing, lyophilization, and packaging).

- Formulation process. Description of the formulation process, the in-process controls, acceptance criteria and the critical steps identified. Information regarding any pooling of bulks or intermediates should be provided.

- Filling process. Description of the filling process, the process controls, acceptance criteria, and the critical steps identified.

- Reprocessing. Description of the procedures established for reprocessing the drug product or any intermediate product, criteria and justification.
- Storage and shipping conditions. When applicable, identify the type and working capacity of the equipment used, areas and buildings (if pertinent), and describe the shipping and storage conditions for the drug product. Additional information should be provided in 3.2. A.1.
- 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 biological product, 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 biological product 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., biological product, packaging component should be submitted.

The process validation report should include inter alia the following:

a) A reference to the current master production document.
b) A discussion of the critical equipment.
c) The process parameters that can affect the quality of the biological product (critical process parameters (CPPs)) including challenge experiments and failure mode operation.
d) 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).
e) The testing parameters/ acceptance criteria including in-process and release specifications and comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies.
f) The analytical procedures or a reference to the appropriate section(s) of the dossier.
g) The results/data obtained.

(Refer to EMA/CHMP/CVMP/QWP/BWP/70278/2012)

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 encephalopathies (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 3. (3.2.A).

3.2.P.4.2 Analytical procedures

Description or bibliographic reference of the analytical methods used to control all the excipients used 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 where applicable.

3.2.P.4.5 Excipients 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

For excipient(s) used for the first time in a drug product or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data (nonclinical and/or clinical) should be provided according to the drug substance format. (Details in 3.2.A.3).

3.2.P.5 Control of the finished biological product

3.2.P.5.1 Specifications of the 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), please 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 biological product should be provided.

3.2.P.5.6 Justification of specifications

Justification of the proposed biological 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 biological product should be provided.

3.2.P.7 Container Closure System

A 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 the 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 possible.

For 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.

The description should also be used on the specialized devices used to monitor the 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 the 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 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 in 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.

N.B: The Authority recommends that a Biological Product to be registered in Rwanda should not exceed 60 months (5 years) of shelf life.

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 the stability of drug products, 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 ongoing stability program should be provided. This should include the protocol to be used, the 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.
(Refer WHO TRS 999, Annex 2;
http://www.who.int/biologicals/areas/vaccines/Annex_2_WHO_Good_manufacturing_practices_for_biological_products.pdf?ua=1).

3.2.A APPENDICES

3.2.A.1 Literatures References: Appendices

Provide key literatures reference used, if applicable.

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.

Non-viral adventitious agents

Detailed information should be provided on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents, bacteria, mycoplasma, fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

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 **(Refer to Q5A, Q5D, and Q6B for further guidance).**

3.2.A.3 Excipients

This appendix is required where applicable.

Novel Excipients - For any novel excipient, including adjuvants, preservatives and stabilizers, used for the first time in a drug product for human use or for a new route of administration, information to support the quality, safety, and suitability for use should be provided in this appendix.
This section should be submitted according to the active substance and/or drug product CTD format described in this document along with cross references to nonclinical studies (Module 4) and clinical studies (Module 5) supporting the safety of a novel excipient.

Other Excipients - Any extensive drug substance and/or drug product information, which is necessary to support the quality, safety, suitability for use, and „approvability" of any (non-novel) non-compendial excipient, and/or any excipient of human or animal origin, should also be provided in this section.

3.2.R Executed and Master batch manufacturing record

Submit Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application. In addition, submit master production document(s) for the proposed production batch size(s).

MODULE 4: NON-CLINICAL STUDIES

Non-clinical studies should comply with the World Health Organization's Guidelines on Non-Clinical Evaluation, WHO Technical Series No. 9984, 2014, or most recent version.

Pre-clinical testing is a prerequisite to moving biological products from the laboratory to the clinic and includes all aspects of testing such as product characterization, proof of concept of effectiveness and safety testing in animals conducted prior to clinical testing in humans.

The submission in this section should be organized as summarized below:

4.1 Table of contents of module 4

4.2 Reports on studies

- 4.2.1 Pharmacology
  - 4.2.1.1 Primary Pharmacodynamics
  - 4.2.1.2 Secondary Pharmacodynamics
  - 4.2.1.3 Safety Pharmacology
  - 4.2.1.4 Pharmacodynamic Drug Interactions
- 4.2.2 Pharmacokinetics (when applicable)
  - 4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
  - 4.2.2.2 Absorption
  - 4.2.2.3 Distribution
  - 4.2.2.4 Metabolism
  - 4.2.2.5 Excretion
  - 4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
  - 4.2.2.7 Other Pharmacokinetic Studies
- 4.2.3 Toxicology
  - 4.2.3.1 Single-Dose Toxicity (in order by species, by route)
  - 4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetic evaluations)
  - 4.2.3.3 Genotoxicity
    - 4.2.3.3.1 In vitro
    - 4.2.3.3.2 In vivo (including supportive toxicokinetic evaluations)
  - 4.2.3.4 Carcinogenicity (including supportive toxicokinetic evaluations)
    - 4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
    - 4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
    - 4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetic evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

4.3 Literature References

Refer to ICH M3(R) and ICH S6.

MODULE 5: CLINICAL STUDIES

This section details particulars of tests which have been performed in human beings regarding the efficacy of the finished biological products and the indications for which it will be used (clinical trials).

Clinical studies shall be designed and conducted to meet WHO and ICH GCP guidelines.

Tabulated summary of the clinical development program of the biological, in which critical parameters that may have changed during the clinical development.

Clinical summary: Provide detailed summary and interpretation of the safety and efficacy data obtained from clinical studies that supports the current prescribing information.

Clinical Expert Report: Applicant shall provide an independent clinical expert report on the clinical studies (evidence of expertise and independence should be provided)

This module recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as ―not applicable or ―no study conducted should be provided when no report or information is available for a section or subsection.

Reference:

1. WHO TRS 987, *Annex 4 Guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology or most current version*.

2. WHO TRS 850 (1995), *Annex 3: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products or most current version).*

REPORTS ON CLINICAL STUDIES

The submission in this section should be organized as summarized below: -

5.1 Table of contents of module 5

5.2 Reports of Clinical studies

5.2.1 Phase I studies
5.2.2 Phase II studies
5.2.3 Phase III studies
5.2.4 Special considerations
5.2.5 Phase IV studies

POST MARKET SURVEILLANCE FOR BIOLOGICAL PRODUCT

In this section, applicant should provide the following post approval commitments:
a) Periodic safety update report (PSUR) in accordance with ICH Guideline E2C (R2) Periodic benefit-risk evaluation report (PBRER).

b) Risk management plan in the format prescribed as per ICH Q 10 (Risk management plan guidelines) and *WHO guidelines on the quality, safety and efficacy of biotherapeutic protein products prepared by recombinant DNA technology, 2013.*

ENDORSEMENT OF THE GUIDELINES

	Prepared by	**Checked by**		**Approved by**
Title	**Division Manager**	**Head of Department**	**Quality Assurance Analyst**	**Director General**
Names	Mrs. Clarisse IRASABWA	Dr. Vedaste HABYALIMANA	Theogene NDAYAMBAJE	Prof. Emile BIENVENU
Signature			Theogene Ndayambaje	
Date	Digitally signed by Clarisse Irasabwa Date: 2024.02.26 16:00:59 +02'00'	Digitally signed by Vedaste Habyalimana Date: 2024.02.26 17:37:06 +02'00'	Digitally signed by Theogene Ndayambaje Date: 2024.02.26 18:01:24 +02'00'	Digitally signed by Rwanda FDA (Director General) Date: 2024.02.27 17:12:37 +02'00'

ANNEXES

< 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:

ANNEX I: COVER LETTER

☐ CTD format documents

☐ 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- PRODUCT REGISTRATION APPLICATION FORM

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 Biological Product application New Biosimilar Extension application Duplicate license Renewal* * If variation has been made, information supporting the changes should be submitted. See Rwanda FDA variation guidelines for registered pharmaceutical products.
1.2	Proprietary Name
1.3	International Non-proprietary Name (INN) of the Active Substance
1.4	Strength of Active Substance per unit dosage form:
1.5	Name and address (physical and postal) of Applicant
(Company) Name: Address: Country: Telephone: Telefax: E-Mail:	
1.6	Name and address (physical and postal) of Local Technical Representative
(Company) Name: Address: Country:	

Telephone: Telefax: E-Mail:	
1.7	Pharmaceutical Dosage form and route of administration
1.7.1	Dosage form:
1.7.2	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):
1.10.1	Proposed shelf life (after reconstitution or dilution):
1.10.2	Proposed shelf life (after first opening container):
1.10.3	Proposed storage conditions:
1.10.4	Proposed storage conditions after first opening:
1.11	Other sister pharmaceutical products registered or applied for registration
1.11.1	Do you hold Marketing Authorization (s) of other Biological product(s) containing the same active substance (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):
1.11.2	Have you applied for Marketing Authorization of Biological product (s) containing the same active substance (s) in the EAC? ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Indication(s):
1.12	Pharmacotherapeutic group and ATC Code
1.12.1	Pharmacotherapeutic group:
1.12.2	ATC Code: (Please use current ATC code)

1.12.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐
1.13	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)
1.14	Country of origin:
1.15	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:

1.16	List ICH and Observers where the product is approved.
1.17	Name(s) and complete physical address(es) of the manufacturer(s)

1.17.1	Name(s) and physical address(es) of the manufacturing site of the finished drug product including the final product release if different from the manufacturer. Alternative sites should be also declared here. All manufacturing sites involved in the manufacturing process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed. (Add as many rows as necessary)
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.17.2	Name(s) and physical address(es) of the manufacturer(s) of the active Substance(s) (Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites should be listed.
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.18	Name and address (physical and postal) of the Brokers and Suppliers (if applicable)
Name:	

Company name: Address: Country: Telephone: Telefax: E-Mail:	
1.19	Name and address (physical and postal) of the person or company responsible for Pharmacovigilance
Name: Company name: Address: Country: Telephone: Telefax: E-Mail:	
1**.20**	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph e.t.c. used for Finished Pharmaceutical Product.
1.21	Qualitative and Quantitative composition of the active substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g., 1 capsule).

Name of active substance(s)*	Quantity / dosage unit	Unit of measure	Reference/ monograph standard
1.			
2.			
3.			
e.t.c			
Name Excipient(s)			
1.			

2.			
3			
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 active 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:

- Active substance(s):
- Excipient(s):

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

Name:

Company name:

Address:

Country:

Telephone:

Telefax:

E-Mail:

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

Name:

Company name:

Address:

Country:

Telephone:

Telefax:

E-Mail:
2.0 DECLARATION BY AN APPLICANT
I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge. I further confirm that the information referred to in my application dossier is available for verification during GMP inspection. I also agree that I shall carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports to the Authority. I further agree that I am obliged to follow the requirements of Legislations and Regulations which are applicable to pharmaceutical 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 service fees. Name: ……..……. Position in the company:…… Signature: ……..…… Date:…….. Official stamp:……..

ANNEX III- EXPERT DECLARATION FORM

The following is an example of a suitable declaration form:

Quality /Non-clinical /Clinical (delete those not appropriate)

I, the undersigned, declare that I have:

i. the suitable technical or professional qualifications to act in this capacity (for more information, refer to the enclosed *curriculum vitae*).
ii. fully examined the data provided by the applicant and have provided references to the literature to support statements made that are not supported by the applicant's original data. This report presents an objective assessment of the nature and extent of the data.
iii. provided a report based on my independent assessment of the data provided.
iv. based my recommendations, regarding suitability for registration, on the data provided herewith. I have considered the attached data and have recommended as to suitability for registration of the intended dose forms and presentations according to the proposed product information document.

I further declare that this expert report represents my own view.

Further, I declare the following to be the full extent of the professional relationship between the applicant and myself:

.....

.....

…….....

…….....

ANNEX IV: QUALITY OVERAL SUMMARY (QOS)

Summary of product information:

Non-proprietary name of the finished drug product			
Proprietary name of the finished drug product			
International non-proprietary name(s) of the active substance(s) including form (salt, hydrate, polymorph)			
Applicant name and address			
Dosage form			
Reference Number(s)			
Strength(s)			
Route of administration			
Proposed indication(s)			
Contact information	Name: Phone: Fax: Email:		

2.3. S Active substance (name, manufacturer)

2.3.S.1 General information, starting materials and raw materials

2.3.S.1.1 Nomenclature

(a) WHO or Pharmacopeial name(s)

(b) Biological name

(c) For combination vaccines (names of active substances)

(d) Chemical modification/conjugation of the active substance

2.3.S.1.2 Structure

(a) Structural formula (if applicable)

(b) Schematic amino acids sequence/molecular formula

(c) Relative molecular mass

(d) Spectroscopic data: NMR, IR, LC-MS (where applicable)

(e) HPLC chromatogramme

2.3.S.1.3 General Properties

2.3.S.1.3.1 Physicochemical Characterization

2.3.S.1.3.2 Biological Activity

2.3.S.1.4 General description of the starting materials of biological origin used to obtain or extract the drug substance

2.3.S.1.5 General description of the raw materials

2.3.S.1.6 Analytical certificates signed by the manufacturer and the applicant.

2.3.S.2 Manufacture

2.3.S.2.1 Manufacturer(s)

(a) Name, address and responsibility (e.g., fabrication, packaging, labelling, testing, and storage) of each manufacturer, including contractors and each proposed production site or facility involved in these activities:

Name and address (including block(s)/unit(s))	Responsibility

(b) Manufacturing authorization for the production of API(s) and, where available, certificate of GMP compliance (GMP information should be provided in *Module 1*):

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

(a) Flow diagram of manufacturing process

(b) Narrative description of the manufacturing process (es)

(c) In process holding steps

(d) Description of lot identification system

(e) Description and validation of the inactivation or detoxification process

(f) Description of the purification process

(g) Description of the conjugation process

(h) Stabilization of the active biological substance

(i) Reprocessing (if applicable)

(j) Filling Procedure

2.3.S.2.3 Control of materials

(a) Source, history and generation of cell substrate

(b) Cell Banking system, characterization and testing

2.3.S.2.4 Control of Critical Steps and Intermediates

2.3.S.2.5 Process Validation and/or evaluation

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

b) Outline Validation strategy and scale used to complete studies

c) Reference analytical procedures used for analysis

2.3.S.2.6 Manufacturing Process Development

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

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

2.3.S.3 **Characterization**

3.2.S.3.1 Elucidation of Structure and Other Characteristics

3.2.S.3.2 Impurities

2.3.S.4 **Control of the Active Substance**

2.3.S.4.1 Specifications

2.3.S.4.2 Description of Analytical Procedures

2.3.S.4.3 Analytical Method validation

2.3.S.4.4 Batch analysis

2.3.S.4.5 Justification of Specifications

2.3.S.5 **Reference Standards or Materials (name, manufacturer**)

(a) Source (including lot number) of primary reference standards or reference materials (e.g.Ph.Int., Ph.Eur., BP, USP, in-house)

(b) Characterization and evaluation of non-official (e.g., not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g., elucidation of structure, certificate of analysis)

(c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard)

2.3.S.5 Container Closure system

2.3.S.6 Stability

3.2.S.7.1 Stability Summary and Conclusions

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

3.2.S.7.3 Stability Data

2.3.S.7 DRUG PRODUCT (NAME, MANUFACTURER)

2.3.P.1 Description and Composition of drug product

(a) Description of the finished drug product

(b) Composition of the finished drug product

Component and Quality Standard (and grade if applicable)	Function	Strength (Label Claim)					
		Quant. Per unit or per mL	%	Quant. Per unit or per mL	%	Quant. Per unit or per mL	%
<complete with appropriate titles							
Subtotal 1							
complete with an appropriate title							
Subtitle 2							
Total							

(c) Type of container closure system used for the FPP and accompanying reconstitution diluents, if applicable:

(d) Overages need to be justified – not intended to compensate for inadequate stability or manufacturing process.

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Active Substance

2.3.P.2.2 Drug Product

2.3.P.2.3 Development of the manufacturing process

2.3.P.2.4 Container closure system

2.3.P.2.5 Microbiological Attributes

2.3.P.2.6 Compatibility

2.3.P.3 Manufacture processes of the drug product

2.3.P.3.1 Manufacturer(s)

(a) Name, address and responsibility (e.g., fabrication, packaging, labelling, and testing) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing:

Name and address (include block(s)/unit(s))	Responsibility

(b) Manufacturing authorization, marketing authorization and, where available, WHO-type certificate of GMP (GMP information should be provided in *Module 1*):

2.3.P.3.2 Batch Formula

Largest intended commercial lot size: Other intended commercial lot sizes:

(a) List of all components of the finished drug product to be used in the manufacturing process and their amounts on a per batch basis.

2.3.P.3.3 Description of the manufacturing process

(a) Flow diagram of the manufacturing process

(b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

2.3.P.3.4 Controls of Critical and Intermediates Steps

(a) Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:

Step (e.g. granulation, compression, coating)	Controls (parameters/limits/frequency of testing)

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

2.3.P.4 Control of excipients

2.3.P.4.1 Specifications

(a) Summary of the specifications

2.3.P.4.2 Analytical Procedures

(a) Summary of the analytical procedures for supplementary tests

2.3.P.4.3 Validation of Analytical Procedures

(a) Summary of the validation information for the analytical procedures for supplementary tests (where applicable)

2.3.P.4.4 Justification of Specifications

(a) Justification of the specifications (e.g., evolution of tests, analytical procedures and acceptance criteria, exclusion of certain tests, differences from officially recognized compendia standard(s)):

2.3.P.4.5 Excipients of Human or Animal Origin

(a) For FPPs using excipients without risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:

(b) CEP(s) demonstrating TSE-compliance can be found in:

2.3.P.4.6 Novel Excipients

2.3.P.5 Control of finished biological product

2.3.P.5.1 Specifications of the drug product

2.3.P.5.2 Analytical Procedures of the drug product

(a) Summary or references to analytical procedures

2.3.P.5.3 Validation of Analytical Procedures

(a) Summary or references to the validation information

2.3.P.5.4 Batch analysis

(a) Description of the lots:

Strength and batch number	Batch size	Date and site of production	Use (e.g., clinical, comparability studies etc.)

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

2.3.P.5.6 Justification of Specification(s)

2.3.P.6 Reference Standards or Materials

(a) Source (including lot number) of primary reference standards or reference materials (e.g., Ph.Int., Ph.Eur., BP, USP, in-house) *not* discussed in 3.2.S.5:

(b) Characterization and evaluation of non-official primary reference

(c) Description of the process controls of the secondary reference standard

2.3.P.7 Container Closure System

(a) Description of the container closure systems, including unit count or fill size, container size or volume:

Description (including materials of construction)	Strength/concentration	Unit count or fill size	Container size (e.g. 1ml, 2ml, 5ml, etc.)

2.3.P.8 Stability of the Finished Biological Product

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

(a) Summary of accelerated and long-term testing parameters (e.g. studies conducted):

Storage conditions (◦C, % RH)	Strength and batch number	Batch size	Container closure system	Completed (and proposed) test intervals

(b) Proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable):

Container closure system	Storage statement	Shelf-life

2.3.P.8.3 Post-approval stability program

(a) Stability protocol for *Primary stability batches*, Commitment batches and Ongoing batches

2.3.P.8.3 Stability Data

a) The actual stability results should be provided in *Module 3*.
b) Summary of analytical procedures and validation information for those procedures *not* previously summarized in 2.3.P.5 (e.g. analytical procedures used only for stability studies):
c) Data to support freeze-thaw cycles recommended

2.3.P.8.4 Description of the procedures used to guarantee the cold chain

2.3.A APPENDICES

3.2.A.1 Literature References: Appendices
3.2.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)
3.2.A.3 Excipients
3.2.R Executed and Master batch manufacturing record

ANNEX V-REGISTRATION CERTIFICATE

RWANDA FDA
Rwanda Food and Drugs Authority

Doc No: DD/HMDR/FMT/009
Revision No:1
Effective Date: 29/02/2024

REGISTRATION CERTIFICATE OF HUMAN PHARMACEUTICAL PRODUCT

Made under Law N°. 003/2018 of 09/02/2018 establishing the Rwanda FDA and determining its mission, organization and functioning in its article 9 paragraph 2.

Registration number: Rwanda FDA-HMP-MA-0000

This is to certify that the Human Pharmaceutical Product described below has been registered in Rwanda subject to conditions indicated at the back of this certificate.

Trade Name:

Name of the Active Ingredient(s) and Strength:

Dosage form and Appearance:

Pack size and Packaging type:

Shelf life in months:

Storage Statement:

Distribution Category:

Name of Marketing Authorization Holder:

Name and address of Manufacturer:

Name of Local Technical Representative:

Validity: Five (5) years from the date of approval

Prof. Emile BIENVENU
Director General

Rwanda FDA, P.O.Box:1948 Kigali-Rwanda, Email: info@rwandafda.gov.rw
Website: www.rwandafda.gov.rw, Toll Free:9707

ANNEX V-REGISTRATION CERTIFICATE

Conditions for Human Pharmaceutical Product Registration

1. All changes to the pharmaceutical product must be communicated to the Authority within the framework of the relevant provisions of the variation guidelines in-force.
2. This certificate shall be invalid immediately after the expiry date and the Marketing Authorization Holder shall ensure that application for renewal of registration is made 90 days before expiry of registration.
3. Registered Human Pharmaceutical Product cannot be advertised without prior approval of the Authority.
4. The Human Pharmaceutical Product shall comply with all relevant provisions of Rwanda FDA regulations at all times.
5. The Marketing Authorization Holder shall ensure that the Human Pharmaceutical Product complies with Rwandan labelling and packaging requirements at all times.
6. The Marketing Authorization Holder shall ensure that the manufacturing facilities where a registered Human Pharmaceutical Product is produced comply at all times with Rwanda FDA Good Manufacturing Practice requirements.
7. The marketing authorization holder and Local Technical Representative/distributors shall ensure that pharmaceutical product within their control are stored and transported in accordance with the instructions and information provided in this certificate.
8. The registration of the Human Pharmaceutical Product shall continue to be valid for five (5) years provided that annual retention fee is paid.
9. The Authority reserves the right to withdrawal this certificate when conditions 1 to 8 are contravened and when the risks of using this pharmaceutical product outweighs the benefits or it is in public interest to do so.

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