RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR REGISTRATION OF VETERINARY BIOLOGICAL PRODUCTS

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) was established by the Law N° 003/2018 of 09/02/2018 with a mandate to protect public health through the regulation of human and veterinary medicines, vaccines and other biological products, processed foods, poisons, medicated cosmetics, medical devices, household chemical substances, tobacco and tobacco products. Part of the mission of Rwanda FDA is to ensure the quality, safety, and efficacy of Veterinary Products including Veterinary Biological Products to protect animal health, and public health in general, from falsified and substandard Products.

In consideration of the provisions of the technical regulations N^{o} DFAR/HMDAR/TRG/001 governing the registration of pharmaceutical products, which recommends issuing guidelines. The authority has issued revised *Guidelines N^{o} DD/VMDR/GDL/004 for registration of Veterinary Biological Products* on the Rwandan market.

The present guidelines have therefore been reviewed in order to cope with the new developments in line with the requirements for marketing authorization of veterinary biological products using the Common Technical Document format. They provide guidance on the required data and information that is needed in an application dossier, and evidence to show that the veterinary biological product meets the quality, safety, and efficacy standards required for biological products to be used in animals.

Rwanda FDA acknowledges the effort of staff who have contributed to the development of these guidelines and is grateful to all stakeholders who participated in the validation of this document.

Prof. Emile BIENVENU
Director General

DOCUMENT DEVELOPMENT HISTORY

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Document Revision History

Revision number	Changes made and/or reasons for revision
Rev 0	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) Editorial changes

TABLE OF CONTENTS

ACCRONYMES AND ABBREVIATIONS

ATC vet code	Anatomical Therapeutic Chemical code. This is a classification system for veterinary medicinal products
BMRs	Batch Manufacturing Records
CTD	Common Technical Document
CVMP	Committee for Veterinary Medicinal Products
DNA	Deoxyribonucleic Acid
EAC	East African Community
EMA	European Medicines Agency
INN	International Non-proprietary Names
MCB	Master Cell Bank
MCS	Master Cell Seed
Ph. Eur.	European Pharmacopoeia
rDNA	ribosomal DNA (Deoxyribonucleic acid)
Rwanda FDA	Rwanda Food and Drugs Authority
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products.
WCB	Working Cell Bank
WCS	Working Cell Seed
WOAH	World Organization for Animal Health

GLOSSARY / DEFINITIONS

For these guidelines, the following definitions shall apply:

Anti-drug antibody: An antibody that binds to the active substance of a biotherapeutic product.

Anti-product antibody: An antibody that binds to the active substance, impurities or excipients of a biotherapeutic product.

Applicant: The Person or company that submit an application for a Marketing Authorization (registration) or license to sell a medicinal product, an update or amendment to existing marketing authorization. Once the marketing authorization is granted, the applicant becomes the Marketing Authorization Holder for that particular medicinal product.

Authority: Means Rwanda Food and Drugs or its acronym "Rwanda FDA", established under Article 2 of the Law.

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 homogeneous. To complete certain stages of manufacture, it may be necessary to divide a batch into a number of sub batches, which are further processed in one process or a series of processes, so that each sub batch can be expected to be homogenous.

Biomarkers: A laboratory measurement that reflects the activity of a disease process, correlates (either directly or inversely) with disease progression, and may also be an indicator of therapeutic response. A genomic biomarker is a measurable DNA and/or RNA marker that measures the expression, function, or regulation of a gene.

Biotherapeutic: A biological medicinal product with the indication of treating diseases.

Comparability exercise: The activities including study design, the conduct of studies, and evaluation of data that are designed to investigate whether a pre-change product and a post-change product are highly similar.

Critical quality attribute: A physical, chemical, biological or microbiological property or characteristic that is selected for its ability to help indicate the consistent quality of the product within an appropriate limit, range, or distribution to ensure the desired product quality.

Distributor: means an organization or an entity, such as a wholesaler that distributes manufacturer's products to market. They serve as an intermediary in the manufacturer's supply chain. promoting and selling the products to wholesalers or other entities, excluding the end consumer. Distributors are authorized to exclusively sell medical products for which they are the legal representatives to other wholesalers.

Drug product: A pharmaceutical product type in a defined container closure system that contains a drug substance, generally in association with excipients.

Drug substance: Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. 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.

Excipient: Any pharmacologically inert substance used for combining with an active substance to achieve the desired bulk, consistency, etc.

Impurity:

a) Any component of the new drug substance which is not the chemical entity defined as the new drug substance.
b) Any component of the drug product which is not the chemical entity defined as the drug substance or an excipient in the drug product

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

In-silicomodeling: A computer-simulated model.

Local Technical Representative: means a registered company in Rwanda and authorized by Rwanda FDA to operate as a wholesale and/or distributor that has received a mandate from the applicant to act on his/her behalf with regard to matters pertaining to registration of the regulated products.

Marketing Authorization /registration certificate:

a) approval from the authority necessary to market and sell a product in Rwanda. This is a legal document that establishes the detailed composition and formulation of the product and the pharmacopoeia or other recognized specifications of its ingredients and of the final product itself, and includes details of packaging, labelling and shelf-life.
b) A legal document issued by the Authority for the purpose of marketing or free distribution of a product after evaluation for safety, efficacy and quality.

Marketing Authorisation Holder (MAH): A person granted with a marketing Authorization of a product by an NRA.

Master cell bank (MCB): 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.

Primary Cell Cultures: Cultures of cells, essentially unchanged from those in the animal tissues from which they have been prepared and being no more than 5 in vitro passages to production level from the initial preparation from the animal tissue.

rDNA-derived biological: Biological product prepared by recombinant DNA technology.

Recombinant DNA technology: Technology that joins together (i.e., recombines) DNA segments from two or more different DNA molecules that are inserted into a host organism to produce new genetic combinations. It is also referred to as gene manipulation or genetic engineering because the original gene is artificially altered and changed. These new genes, when inserted into the expression system, form the basis for the production of rDNA-derived protein(s).

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.

Veterinary Biologicals: Products of biological origin other than immunological products intended to be used in animals to promote their health and wellbeing. They include a wide range of products such as hormones, pheromones, blood and blood components, allergenic, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins. They can be composed of sugars, proteins, or nucleic acids, or complex combinations of these substances, or maybe living entities such as cells and tissues or a substance of synthetic origin that is manufactured, sold, or represented for use in restoring, correcting, or modifying organic functions in animals. Biologicals are isolated from a variety of natural sources: human, animal, or microorganism and may be produced by biotechnology methods and other cutting-edge technologies.

Wholesaler: An entity that is authorised to carry on the business of selling medical products in large quantities to other authorised sellers with the exception of dispensing or providing medical products directly to a patient.

Withdrawal period: The minimum time that must elapse between the cessation of treatment of a food-producing animal and either the slaughter of the animal for human consumption or the resumption of the supply for human consumption of products, such as eggs, milk derived from the animal.

Working cell bank (WCB): The working cell bank is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the master cell bank under defined culture conditions.

1. INTRODUCTION

1.1. Background

In pursuance of Law No 003/2018 of 09/02/2018 establishing Rwanda Food and Drugs Authority, determining its mission, organization, and functioning, especially in article 9. Considering the provisions of the technical regulation No DFAR/HMDAR/TRG/001 governing the registration of medicinal products. The authority issues a *revised "Guidelines No: DD/VMDR/GDL/004 for registration of veterinary biological products".*

These guidelines were developed to guide applicants who intend to register biological products for veterinary use in Rwanda. These guidelines apply only to veterinary biological products other than immunological products intended to be marketed in Rwanda. Veterinary biologicals include but not limited to a range of products such as hormones, pheromones, enzymes, vitamins, blood and blood components, allergenic, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins.

They describe information required to demonstrate that a veterinary biological product intended to be marketed in Rwanda complies with the established requirements on quality, safety, and efficacy in addition to administrative information to be included in the application dossier. The Guidelines also set out procedures and requirements for the application for registration of veterinary biological products using the Common Technical Document (CTD).

The CTD has five Modules as mentioned below:

Module 1: Administrative Requirements

Module 2: Overviews and Summaries

Module 3: Quality Requirements for Active Substance and Finished Product

Module 4: Non Clinical Studies

Module 5: Clinical Studies

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.

Note that the applicants should not modify the overall organization of the CTD.

1.2. Scope

These guidelines apply only to veterinary biological products other than immunological products intended for marketing in Rwanda. It also assists the Authority during the full assessment and registration of VPPs.

1.3. Preparation and Presentation of Information in CTD format

The applicant shall prepare and present the product's information dossier in the CTD format according to the requirements as stipulated below:

a) The application should be written 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 of appendices
c) The Quality Overall Summary (QOS) should be formatted as a word document Downloadable on Authority's website (**Appendix 6**) and the body data in Module 3 should be in PDF.
d) All pages of the application should be numbered in the style: **page x of y.**
e) The PDF documents should be in Optical Character Recognition (OCR), selectable and searchable.

A separate application is required for each product that differs in active ingredient(s), strength, dosage form, proprietary names though containing the same ingredients or is considered to be different products. However, products containing the same active ingredients and the same strength made by the same manufacturer at the same manufacturing site, to the same specifications and dosage form, but differing only in packing or pack sizes require only one application.

1.4. Submission of application

All applications for registration of veterinary biological products for either locally manufactured or imported shall be submitted via Rwanda FDA Integrated Regulatory Information Management System (IRIMS CLIENTS) available on Rwanda FDA website (https://www.irims.rwandafda.gov.rw/portal/).

Any applicant who is not resident in Rwanda shall appoint a local technical representative (LTR) who must be a company incorporated in Rwanda and licensed by Rwanda FDA as a wholesaler and/or distributor to deal with regulated products.

1.5. Application requirements

An application dossier for registration of veterinary biological products in Rwanda shall include the following:

1. Dated and signed cover letter (**Appendix 1**);
2. Dated and signed application form for product registration (Appendix **2**);
3. The proof of payment for product registration fee in accordance with regulations No: ODDG/RES/TRG/001 Governing Tariff/Fees and Charges on Services Rendered by Rwanda Food and Drugs Authority;
4. CTD Format in (PDF) and QOS in MS Word;
5. Two commercial samples of each pack size with respective Certificates of Analysis (CoAs);
6. Rwanda FDA GMP certificates or Proof of payment for Rwanda FDA GMP inspection and application for GMP inspection to Rwanda FDA.

1.6. Officially Recognized References

The official pharmacopoeias recognized 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 in accordance with the current edition of compendia.

1.7. 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 Organization for Animal Health (WOAH) and the Veterinary International Conference on Harmonization (VICH). Where specific guidelines are unavailable, Rwanda FDA adopts Committee for Veterinary Medicinal Products (CVMP) Guidelines, which are available at the following websites EMA: https://www.ema.europa.eu/en/ and Veterinary International Conference on Harmonization (VICH) Guidelines: https://www.vichsec.org/en/.

1.8. Rwanda FDA Dossier Assessment Procedures

1.8.1. Dossier assessment for product quality, efficacy, and safety

After Rwanda FDA receives a complete product application dossier, the application will be scheduled for assessment according to the First In First Out (FIFO) rule. Priority assessment may be granted where the product is intended for treatment of rare disease conditions or in the case of emergency situation. For more details, refer to Guidelines for conditional approval of veterinary products. Furthermore, an abridged assessment may be conducted in case a product is eligible for the reliance procedure using the guidelines on reliance for regulatory decision making and the guidelines for abbreviated assessment procedures for registration of veterinary products.

A product dossier is assessed by two assessors to provide scientific and regulatory oversight regarding the quality, safety, and efficacy of the product under assessment. There might be cases where the application dossier deems necessary to be assessed by more than two assessors for full assessment. Rwanda FDA reserves the right to request any additional information to establish the quality, safety, and efficacy of a veterinary biological product. 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 clock 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 the third time and the applicant provides unsatisfactory responses, the application will be rejected (Figure 1).

If the responses to the queries are not submitted within ninety (90) working days 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.

1.8.2. Compliance with the Good Manufacturing Practices (GMP)

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 GMP regulations and guidelines before a product is registered. No product shall be registered unless the facility complies with GMP. More information on GMP requirements and application for GMP inspection is detailed in the Rwanda FDA Guidelines on Good Manufacturing Practices and its annexes downloadable from the Rwanda FDA website.

1.8.3. Internal Scientific Review Committee for Product Registration

After the completion of the product dossier assessment, a final assessment report shall be presented to the Internal Scientific Review 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 all raised issues are resolved. 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 Veterinary Biological products will be granted. The registration shall be valid for a period of five (5) years. If Rwanda FDA suspends or cancels the registration, a written official communication shall be made to the applicant.

1.9. Timelines for product registration

Product dossiers shall be scheduled for assessment according to the First In First Out (FIFO) rule upon compliance of the requirements. A new application shall be processed **within twelve (12) months** from the receipt of the application. Once a query has been issued to the applicant, the assessment process clock stops until Rwanda FDA receives a response to the raised queries.

Figure 1. Graphical illustration of timeline

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative documents (for example, application forms and certifications), labeling, general correspondence and annexes. Documents should be organized in the order listed below. Generally, all of the documents in Module 1, other than the annexes,

should be provided in a single volume. The annexes to the module should be submitted in separate volumes.

1.1 Comprehensive table of content for all modules

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.

1.2 Cover Letter

A dated and signed Cover Letter should be submitted in the IRIMS with the product dossier clearly indicating the product name seeking a Marketing Authorization and the contact details of the applicant (Refer to appendix 1).

1.3 Application form

An application to register a veterinary biological product must be accompanied by a completed Application Form (**Appendix 2**). The application form should be duly filled with relevant information and attachments, dated, signed, and stamped appropriately.

1.4 Manufacturing and Marketing Authorization

A valid manufacturing license/authorization or a valid Certificate of Pharmaceutical Product (CoPP), or an equivalent certificate issued by a competent authority of the country of origin to the manufacturer of the finished biological product should be submitted.
If applicable a valid manufacturing authorization for the production of the diluent should also be provided. In addition, valid manufacturing authorization(s) for the active ingredient (s) manufacturer (s) should be provided.

1.5 Mock-Ups

Mock-ups of the sample(s) presentation of the veterinary biological product available at the time of initial application should be submitted.

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.

1.6 Summary of Product Characteristics (SmPC)

A summary of characteristics of the veterinary biological product under evaluation should be submitted. The SmPC should be prepared following the content and the format as provided in **Appendix 3**.
After the assessment and the approval of the submitted SmPC, the latter will be published online. The consent from the applicant can be requested if applicable.

1.7 Container Labeling

Containers should be labelled as recommended in **Appendix 4** of this guideline. This should be provided as mock-ups

1.8 Product Information Leaflet (PIL)

Every container of Veterinary Biological Products should be accompanied by an information leaflet. One copy of the information leaflet prepared based on the provisions of **Appendix 5** should be provided.

1.9 Product Samples

Two Samples of the finished product with their certificates of analysis, labels, and cartons of the primary and secondary packaging of the product, including the package insert and accessories should be provided. The number of samples can increase depending on the nature and type of the product applied for registration, ideally, samples should be provided to allow full monograph analysis. The submission of samples should comply with the storage conditions as prescribed by the manufacturer to avoid any alteration of the product during transportation.
Those samples should be accompanied by a cover letter clearly stating the application reference number generated by Rwanda FDA portal at the time of submission.

1.10 List of Countries where the Product has been Licensed and Summary of Approval Conditions

If applicable, the applicant should provide the list of countries where the product is registered at the time of the application for registration. In the event the product has been registered in other countries, copies of registration certificates should be attached.

1.11 Good Manufacturing Practice (GMP)

A valid certificate of GMP compliance should be provided. This should include manufacturers that are involved in any stage of the production process, for example, the manufacturer(s) of the finished biological product, active ingredient (s), the diluents, and those responsible for labeling and packaging of the finished biological product.

In addition, a copy of a GMP certificate issued by Rwanda FDA or proof of application and proof of payment, to GMP inspection of the finished veterinary biological product manufacturing site by Rwanda FDA should be submitted.

1.12 Authorization of the Local Technical Representative

Any applicant who is not resident in Rwanda shall appoint a local technical representative (LTR) who must be a company incorporated in Rwanda and must be authorized by Rwanda FDA to operate as a wholesale and/or distributor that has received a mandate from the applicant to act on his/her behalf with regard to matters pertaining to registration of the regulated products.
The appointment shall be notified to the Authority by submitting a letter of appointment supported by original copy of power of attorney duly notarized in country of origin, and a valid copy of the license issued by Rwanda FDA.

1.13 Certificates of Suitability of monographs of the European Pharmacopoeia (CEP) or APIMF

If CEP is available, applicants should present a copy of CEP and a Letter of Access to CEP as appropriate. Where reference is made to an Active Pharmaceutical Master File (APIMF), the applicant should provide the APIMF and a Letter of Access to the APIMF as appropriate.

MODULE 2: OVERVIEWS 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, 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 the following order:

2.1 A table of contents.

A table of content of module 2 should be provided.

2.2 Introduction

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

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 other modules of the registration document. This section should follow the format specified in the Quality Overall Summary template (**Appendix 6**).

2.4 Overview and summary of the nonclinical studies

A comprehensive and critical assessment of the results of the evaluation of the biological product in a controlled environment to support the safety and efficacy of the product should be presented.
An overview and summary of the results of the pharmacological, pharmacokinetic, and toxicological tests should be presented.

2.5 Overview and summary of the clinical studies

This section should include a critical analysis of the clinical study results included in the clinical summary and in module 5. Information should include a 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 in relation to 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:

1. Introduction
2. Detailed discussion of the product development
3. Overview and summary of the mechanism of action
4. Overview and summary of the efficacy
5. Overview and summary of the safety
6. Conclusions on risk/benefit analysis
7. Literature References

MODULE 3: QUALITY (CHEMISTRY, MANUFACTURING, AND CONTROLS)

3.1 Table of contents of module three

3.2.S Active substance

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

3.2.S.1 General information

3.2.S.1.1 Nomenclature

Information concerning the nomenclature of the active substance (e.g. proposed INN name, Pharmacopoeial name, proprietary name, company/laboratory code (could include trademark name), other names or codes, if any), and identification number of production strain 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 a biological product 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.

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 the creation, testing, and storing of the cell banks should be listed.

3.2.S.2.2 Description of the manufacturing process and process control

Information on the manufacturing process should be presented in the form of a flow diagram that 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. The explanation should be provided on batch numbering system and any pooling of harvest or intermediates as well as the 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 induction.
iv. Information with respect to operating parameters for each stage with links to in-process controls or specifications.

b. Purification

The following information should be provided:

i. Flow diagram from crude harvest, extraction, and purification to final step to obtaining final active substance.
ii. Information for each stage should be provided (pH, conductivity, processing times, hold times, elution profiles, fraction (selection) including viral inactivation step(s) if applicable.
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 action.

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.

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 should be summarized and detailed information should be provided.

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.

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 the 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 the 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.

3.2.S.2.4 Control of Critical Steps and Intermediates

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

3.2.S.2.5 Process Validation and/or evaluation

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

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

b. Outline Validation strategy and scale used to complete studies

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

c. Reference analytical procedures used for analysis

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

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

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

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

The description of change(s) made to the manufacture of drug substance batches used in support of the 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) in relation to the change should also be provided.

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

The significance of 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 substance should be provided along with a discussion of the data including a justification for selection of the test and assessment of results.

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.

iii. Process Characterization shall include

- Establishment of operating parameters and in process controls for commercial scale manufacture.
- Elimination of operating parameters/in process controls based on development work that deemed them non-critical.
- Freeze/thaw development data used to set number of cycles for drug substance.
- Post approval – Comparability assessment of current to proposed change including side-by-side batch release data, Co-mixture analysis with reference standard and subset of initial 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.

3.2.S.3 Characterization of veterinary biological active substance

3.2.S.3.1 Elucidation of structure and other characteristics

Information on the physicochemical and/or biological characterization should be provided.
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, and purity.

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 that 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 drug substance shall include appearance, and description, identity, purity, and potency. Information on the source, including, as appropriate species of animal, type of microorganism should be included in the specifications, etc. (Refer to VICH GL40).

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 the specification is "Comparable to Reference Material".

3.2.S.4.5 Justification of Specification

Justification for the active substance specification should be provided.
Rationale for use of tests for specific quality attributes taking into account the specifications and linking to 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 of Reference standard or material used for testing of active substance should be provided. The information should include a description of the manufacturing process of the reference standard, and where appropriate the 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 drug substance should be provided, including specifications for their component materials. The specifications should include description and identification (and critical dimensions with drawings where appropriate). Suitability and compatibility of the materials of construct with active substance should also be demonstrated, literature reference may suffice when applicable.

3.2.S.7 Stability

Stability studies should include: Storage conditions i.e. Temperature and relative humidity for accelerated and stress Conditions. (Refer to VICH GL17).

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.

3.2. P. FINISHED BIOLOGICAL PRODUCT

This section should contain information on the final product including all drug substances and excipients. If any proprietary preparation or mixtures are used as components, a complete statement of composition and other information that will properly describe and identify these materials should be provided.
For all ingredients of human or animal origin, the testing results or certificates of analysis demonstrating freedom from adventitious agents should be provided.

3.2. P.1. Description and composition of the biological 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 diluent (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 the manufacturing process.
A table can 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 program should be explained and justified. A link between formulation development and clinical batches should also be provided.
Supportive data and results from specific studies or published literature may be included within or attached to the Pharmaceutical Development Section. Additional supportive data may be referenced to the relevant non-clinical sections of the application. The report should include the following:

3.2.P.2.1 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 the final qualitative/quantitative formula of the biological product should be provided.

3.2.P.2.3 Development of the manufacturing process

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

3.2.P.2.4 Container closure system selected

Information on the materials selected, protection against humidity and light, compatibility of the materials should be provided.
Information on the suitability of the container closure system used for the storage, transportation (shipping), and use of the drug product should be discussed. Results of the extractable study should be presented and depending on the results, also a leachable study with e.g. a 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 biological 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.

3.2.P.3.3 Description of the manufacturing process

- A flow diagram should be presented giving the steps of the process, indicating the points where materials enter the process. The critical steps and points at which process controls, intermediate tests, or final product controls are conducted should be identified.
- A narrative of the manufacturing process, equipment and materials used, the room or area where the operation is performed (may reference the simple floor diagram), in-process controls, and the critical points identified should be provided.

3.2.P.3.4 Control of critical and intermediate steps

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

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

Description, documentation, and results of the studies on validation and/or evaluation of the manufacturing process, should be provided for the critical steps or critical tests employed in the manufacturing process.
A product quality review may be submitted in place 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.
c. The applicant should submit a written commitment that information from these studies will be available for verification.
d. Validation information relating to the adequacy and efficacy of any sterilization process (e.g. medicinal 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 (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 including 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 appropriate section(s) of the dossier.
g. The results/data obtained.

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

3.2.P.3.6 Description of the batch identification system

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

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

Information on the specifications for all the excipients employed in the formulation should be provided. List of raw materials meeting in-house specifications including the tests performed and specifications of Biological starting materials with information on the requirements to avoid the risk of transmissible spongiform encephalopathies (TSEs) in the final product including Certificate of Suitability (CEP) should be included.

3.2.P.4.2 Analytical procedures

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

3.2.P.4.3 Validation of the analytical procedures

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

3.2.P.4.4 Justification of specifications

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

3.2.P.4.5 Substances of Human or Animal Origin

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

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

3.2.P.4.6 Novel excipients

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

3.2.P.5 Control of the finished biological product

3.2.P.5.1 Specifications of the biological product

Specifications for the biological product should be provided. At minimum, specifications should contain test and acceptance criteria for description and appearance, identity, quantity, potency, purity, and impurities. For Intermediate Products (as appropriate): Highlight the list of the routine tests performed and specifications for intermediates.

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

Detailed information on the analytical procedures used for quality control of the biological 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 biological product, including experimental data should be provided. This information should include a 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 specifications 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 the 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 the finished biological product should be provided.

3.2.P.7 Container Closure System

Detailed description of the container closure system used for the biological 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 auto injector), 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.

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 Biological 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 biological product prepared from different lots of active 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 VICH GL 17.

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.

3.2.P.8.3 Stability data

Evidence should be provided to demonstrate that the product is stable for the proposed validity period under the indicated storage conditions. The stability of each dosage form should be separately documented.
The summary results, which support the proposed expiration-dating period, under recommended conditions, in the final container and closure system, should be provided.

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

a. Information on stability of drug product, quality control methods and rationale for the choice of tests for determining stability.
b. Information on the dates of manufacture of the lots, the lot numbers, the vial and dose size, and the scale of production.

For lyophilized products, the data supporting the shelf-life of the product following reconstitution should be included.
If the biological product is frozen, data supporting the stability of the product through a stated number of freeze-thaw cycles should be provided.

A plan for an on-going stability program should be provided. This should include the protocol to be used, number of final lots to be entered into the stability protocol each year and how such lots will be selected. A stability study protocol should be provided.

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

3.2.P.8.4 Shipping

Details should be provided on the measures used to guarantee the adequacy of temperature and humidity conditions for shipping the biological 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. The declaration should be signed by quality control personnel.

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.

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 biological product for veterinary 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 active substance and/or biological 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

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 Pharmacodynamics studies
4.2.2 Pharmacokinetics (when applicable)
4.2.3 Toxicology
- 4.2.3.1 General toxicology information
- 4.2.3.2 Special toxicology
- 4.2.3.3 Toxicity of new substances used in formulation (new adjuvants, stabilizers, additives).

4.2.4 Special Considerations

4.3 Literature References

MODULE 5: CLINICAL STUDIES

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

5.1 Table of contents of the Module

5.2 Reports on Field Trial

5.2.1 Efficacy Study
5.2.2 Safety Study

5.3 Animal Ethics Committee Approval

5.4 Special Consideration

5.5 Bibliographic references

ENDORSEMENT OF THE GUIDELINES

	Prepared by	**Checked by**		**Approved by**
Title	**Division manager**	**Head of Department**	**QMS Division Manager**	**Director General**
Names	Dr. Doreen INGABIRE	Dr. Vedaste HABYALIMANA	Ms. Marie Ange UWASE	Prof. Emile BIENVENU
Signature				
Date				

APPENDICES

ANNEX I – COVER LETTER FOR BVP

< 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 immunological veterinary product that details are as follows:

Name of the Immunological veterinary product(s): …….

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

INN/Active ingredient(s): …….....

ATC Code(s): ……..……...

You will find enclosed the submission dossier as specified hereafter:

☐CTD format document

☐Product Samples

☐We confirm that all future submissions for this specific product will be submitted in this same format

☐The product dossier submitted in IRIMS contains the following modules:

Module 1: Administrative information and product information

Module 2: Overview and summaries

Module 3: Quality

Module 4: Non-clinical Studies

Module 5: Clinical Studies

Type of Submission: ☐Full Application ☐Abridged Application

☐ 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 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>

APPLICATION FORM FOR A NEW MARKETING AUTHORISATION FOR VETERINARY PHARMACEUTICAL, BIOLOGICAL AND IMMUNOLOGICAL PRODUCTS

(Application form Adopted from the Regional Regulatory Harmonization for Livestock Products in Sub-Saharan Africa)

A separate application form is required for each strength and/or pharmaceutical dosage form. Different pack sizes of the same product can be included on the same form.

SECTION 1 - PRODUCT NAME(s)

1.1. Proposed trade name of product

1.2. International Non-Proprietary Name (Generic Name)

SECTION 2 – APPLICATION DETAILS

2.1 Product Type

Please select either pharmaceutical OR Biological/Immunological

☐	Pharmaceutical
☐	Biological *A VMP sourced from a biological source that is not a vaccine*
☐	Immunological - *vaccine.*

2.2 Type of Drug Substance

Please select only one

☐	Newly marketed Product with New Drug Substance
☐	Newly marketed Product with New Combination of Drugs Substances
☐	Newly marketed Product with Existing Drug Substance
☐	Re-evaluation of an Existing Product

SECTION 3 – PRODUCT DETAILS

3.1 Formulation *(provide the full formulation details)*

	Name of the substance	**Concentration in the final product**	**Description of Function** *(example, active substance, attenuated virus, adjuvant, excipient)*
1			
2			

Please add extra rows, if required.

3.9 Proposed Distribution category

Prescription only medicine- Veterinarian (POM-V)	
Prescription only medicine – Veterinarian, Pharmacist, SQP (POM-VPS)	
Authorized Veterinary Medicine- General Sales (AVM-GSL)	
Non- Food Animal- Veterinarian, Pharmacist, SQP (NFA-VPS)	

SECTION 4 – CONTACT INFORMATION

4.1 Details of the proposed Marketing Authorization Holder (MAH) or Applicant contact:

Company Name:	
Company Address:	
Telephone No.	
Email	

4.2 Name, address and contact details of the proposed Manufacturers

4.2.1. Name, address and contact details of the proposed finished product manufacturer(s):

If the proposed named manufacturer is the same as the proposed MAH, simply enter 'same as MAH' in the field below.

	Name, address and telephone number, Email	**Brief description of functions performed** *(e.g. bulk manufacturing, batch release, primary or secondary packaging)*
1		
2		

Please add extra rows, if required.

4.2.2. Name, address and contact details of the proposed manufacturer (s) of Active pharmaceutical ingredient (s) or active Immunogenic Substance(s):

	Name, address and telephone number, Email	**Brief description of functions performed** *(e.g. bulk manufacturing, batch release, primary or secondary packaging)*
1		
2		

Please add extra rows, if required.

SECTION 5 – REGULATORY STATUS

5.1 Regulatory Status in Country of Origin. *Provide the regulatory status in the country of manufacture and the authorisation number/reference.*

5.2 Regulatory Status in Other Territories. *Regulatory status of the proposed product in other countries globally, including successful or pending, rejected, withdrawn, suspended or revoked applications.*

Country/Region with successful authorisations

Please add extra rows, if required.

Country/Region where applications are pending

Please add extra rows, if required.

Country/Region where applications/authorizations have been rejected, withdrawn, suspended or revoked

Please add extra rows, if required.

SECTION 6 – DECLARATION

Contact details of the person responsible for the application: *A legal representative of the applying company to take full responsibility for the application on behalf of the MAH and is answerable to the authority.*

Name:	
Company Name:	
Address (including country):	
Telephone No.	
Email Address:	
Position and Affiliation:	

I confirm that the information provided in support of this application is correct at the time of submission.

I understand that if any information provided in this application is later found to be false or incorrect, the authorization may be suspended or revoked.

SIGNATURE:	
DATE:	

***Note**: - not signing this box will lead to your application being rejected at validation.*

- If fees have been paid, attach proof of payment

ANNEX 1: Rwanda Specific Information

If applications are being made to a number of countries, please provide the following details for each country (please replicate this annex for each country)

A.1 Contact details of in-country Local Technical Representative: *An in-country legal representative of the company holding the original authorization to take full responsibility for the product on behalf of the MAH and is answerable to the authority.*

Name:	

Address (including country):	
Telephone No.	
Email Address:	

A.2 Name and contact details of person responsible for pharmacovigilance:

Name:	
Telephone No.	
Email Address:	

A.3 Proposed Distribution Category in country *(example, controlled drug, drug requiring prescription by veterinarian etc.)*

A.4 Proposed Storage Conditions (*if applicable, also include the proposed storage condition after first opening and after reconstitution*)

A.5 Intended Use

Quality Overall Summary (QOS) for Veterinary Biological Products

GENERAL INSTRUCTIONS

Quality overall summary (QOS) template should be completed for veterinary biological product (VBP) containing active substances. All sections and fields in the QOS template that would be applicable should be completed.

It is understood that certain sections and fields may not apply and should be indicated as such by reporting "not applicable" in the appropriate area with an accompanying explanatory note.
The use of tables to summarize the information is encouraged, where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths), as necessary.
These tables are included as illustrative examples of how to summarize information. Other approaches to summarize the information can be used if they fulfil the same purpose.
Please state the exact location (Annex number) of any appended documents in the relevant sections of the form.

See the "Guidelines for registration of veterinary biological products for general and detailed instructions on the completion of this template.
Should you have any questions regarding this form, please contact the Rwanda Food and Drugs Authority (Rwanda FDA).

2.3 S ACTIVE SUBSTANCE (NAME, MANUFACTURER)

2.3. S.1. General information

2.3.S.1.1 Nomenclature

- Biological name (including strain and/ or clone designation)
- Chemical name
- The name(s) or designation of the strain of organism used to produce the active immunogenic substance

2.3.S.1.2 Structure

- Structural formula
- Schematic amino acids sequence/molecular formula
- Relative molecular mass

2.3.S.1.3 General properties

- Physicochemical Characterization
- Biological Activity

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 the manufacturing process and process controls

1. Flow diagram of manufacturing process
2. Narrative description of the manufacturing process (es)

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 of Veterinary Biological active substance

3.2.S.3.1 Elucidation of Structure and other characteristics
3.2.S.3.2 Impurities

2.3. S.4. Control of Active Substance

2.3.S.4.1 Specification
2.3.S.4.2 Analytical Procedures
2.3.S.4.3 Validation of Analytical Procedures
2.3.S.4.4 Batch Analysis
2.3.S.4.5 Justification of Specification

2.3.S.5 Reference Standard

2.3.S.6 Container Closure system

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions
2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment
2.3.S.7.3 Stability Data

2.3.P FINISHED VETERINARY BIOLOGICAL PRODUCT (NAME, MANUFACTURER)

2.3.P.1 Description and Composition

a. Description of the finished veterinary biological product
b. Composition of the finished veterinary biological 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	%	Quantity per unit or per mL	%
Complete with appropriate titles							
Subtotal 1							
complete with the appropriate title							
Subtotal 2							
Total							

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

2.3. P.2. Pharmaceutical development

3.2.P.2.1 Active Substance
3.2.P.2.2 Drug Product
3.2P.2.3 Development of the manufacturing process
3.2.P.2.4 Container closure system
3.2.P.2.5 Microbiological Attributes
3.2.P.2.6 Compatibility

2.3.P.3 Manufacture processes of the biological product

2.3.P.3.1 Manufacturer(s)

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

Manufacturing authorization, marketing authorization and, where available, certificate of GMP (GMP information should be provided in Module 1).

2.3.P.3.2 Batch formula

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

2.3.P.3.4 Control of critical and intermediate steps

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

Step	**Controls (parameters/limits/frequency of testing)**

2.3.P.3.5 Validation and/or evaluation of the processes
2.3.P.3.6 Description of the batch identification system

2.3.P.4 Control of excipients

2.3.P.4.1 Specifications

Summary of the specifications

2.3.P.4.2 Analytical Procedures

Summary of the analytical procedures for supplementary tests

2.3.P.4.3 Validation of Analytical Procedures

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

2.3.P.4.4 Justification of Specifications

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 Finished biological products 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 the finished biological product

2.3.P.5.1 Specifications of the biological product

2.3.P.5.2 Analytical Procedures of the biological 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, compatibility studies)**

2.3.P.5.5 Characterization and/or determination of impurities
2.3.P.5.6 Justification of specifications

2.3.P.6 Reference standards and materials

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

2.3.P.7 Container Closure System

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, 2 mL, 5 mL. etc.)**

2.3.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

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.8.2 Post-approval stability program

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 3.2.P.5 (e.g. analytical procedures used only for stability studies):

c. Data to support freeze thaw cycles recommended

2.3.P.8.4 Shipping

The procedures used to guarantee the cold chain.

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the veterinary biological product

State the name under which the product will be marketed.

2. Qualitative and quantitative composition

Provide the qualitative and quantitative composition per unit dosage form in terms of the active substance(s) and excipients in a format as indicated below:
Each dose of (product name) contains:

- Active substance(s):
- Adjuvant(s) (if any):
- Excipient(s):

3. Dosage form

State clearly the dosage form of the product. Any descriptive terms to give an indication of the exact type of dosage form should also be included. The visual and physical characteristics of the product also should be stated.

4. Clinical particulars

4.1. Target species

State target species, including any sub-category where appropriate.

4.2. Indications for use

Provide information on indications of the product in the target species.

4.3. Contraindications

State the contraindications for this veterinary biological product e.g. not for use in pregnant animals, very young and old animals.

4.4. Special warnings

State any specific warnings associated with this product.

4.5. Special precautions for use

State precautions to be taken by the person administering the veterinary biological product (if any). State the precautions that should be taken for use in animals.

4.6. Adverse effects following the administration (frequency and seriousness).

State the side effects and adverse reactions of the product. Within each frequency grouping, undesirable effects should be presented in order of decreasing seriousness.

4.7. Use during pregnancy, lactation or lay

Provide information on the use of the product in pregnant, lactating animals or laying birds and the reasons for any relevant recommendation. Information about the use of the product during pregnancy or lactation may have been provided in the sections dealing with contra-indications or special precautions for use. In such cases, a cross-reference to the relevant section will be sufficient.

4.8. Interaction with pharmaceutical or other biologicals and other forms of interaction

State briefly the interactions of the product with other types of medicinal products, or state whether compatible with other biological products likely to be used at the same time.

4.9. Amount to be administered and administration route

State the dose, dosage schedule and route of administration.

4.10. Overdose (symptoms, emergency procedures, if necessary)

Describe symptoms observed at higher dose levels. Give the recommended management and emergency procedures.

4.11. Withdrawal period

State the withdrawal periods (if applicable).

5. Pharmaceutical properties

State the pharmaceutical properties of the product.

6. Biological veterinary product particulars

6.1. Incompatibilities

Provide information on incompatibilities of the product with medicinal and other biological products.

6.2. Shelf life

- Shelf life (in months) of the veterinary biological product.
- State the biological shelf life after reconstitution (where applicable).
- For multi-dose packages state the in use shelf life after first opening (where applicable).

6.3. Special precautions for storage

State the recommended storage conditions (e.g. temperature, light) as established by stability studies. The storage temperature must be stated in figures.

6.4. Nature and composition of packaging

State briefly the type(s) of packing and pack size(s) being applied for registration. The pack sizes declared here should correspond with the samples submitted.

6.5. Special precautions for the disposal of unused products or waste

State Material derived from the use of such products.
Provide practical instructions for the safe disposal of the biological product and waste materials derived from the used/unused products (if applicable).

7. Marketing Authorization holder/License holder

State the name and physical address of the registrant including telephone, fax number and e-mail. In addition, provide the name and physical address of the manufacturer including telephone, fax number and e-mail if different from the Marketing Authorization Holder.

8. Date of revision of the text

To be stated at the time of approval of changes to the SmPC.

CONTAINER LABELING FORMAT

Every immediate and outer container of any veterinary biological product shall be labelled in clearly legible indelible letters in English.

Particulars to appear on the primary package

1. Name of the veterinary biological product
2. Name and quantity of active substance(s)
3. Target species
4. Indication(s)
5. Dosage and administration
6. Contraindications (see the package leaflet)
7. Content by volume or number of doses
8. Storage conditions
9. Date of manufacture, expiry, and batch number in an uncoded form
10. Name and physical address of the finished product manufacturer
11. For Veterinary Use only

For containers of less than or equal to 10 ml capacity that are marketed in an outer pack such as a carton, the outer packaging will bear all the required information while the immediate container will only contain items (1), (2), (3), (5), (7), (8), (9). Alternatively, a logo that unambiguously identifies the company or the name of the dosage form, or the route of administration can be used.

Particulars to appear on the secondary package

1. Name of the veterinary biological product
2. Name and quantity of active substance(s) and excipients
3. Target species
4. Indication(s)
5. Dosage and administration
6. Contraindications
7. Warnings and precautions, “for animal treatment only” “keep out of reach of children” are Mandatory
8. Withdrawal Period (if applicable)
9. Content by volume or number of doses
10. Storage conditions
11. Date of manufacture, expiry, and batch number in an Uncoded form
12. Name and physical address of the manufacturer

Small packs container

As a minimum, the following information is printed directly on blister or/and strip:

1. Name, strength, and pharmaceutical form of the veterinary biological product.
2. Name of the manufacturer.
3. The batch number assigned by the manufacturer.
4. The manufacturing and expiry dates.

PRODUCT INFORMATION LEAFLET (PIL) FORMAT

Particulars to appear on the package leaflet

1. Name of the veterinary biological product
2. Name and quantity of active substance(s) and excipients
3. Indication(s)
4. Contraindications, warnings and precautions
5. Adverse effects following the administration (frequency and Seriousness)
6. Target species
7. Amount to be administered and administration route for each Species
8. Withdrawal period (where applicable)
9. Special storage precautions
   - do not use after the expiry date stated on the <label>, <carton>, <bottle>
   - <shelf-life after first opening the container.>
   - <shelf-life after dilution or reconstitution according to directions.>
   - <do not use the product if you notice {description of the visible signs of deterioration}.>
10. Special warning(s)
11. Content of pack(s) by volume or number of doses
12. Special precautions for the disposal of unused product or waste materials, if any (dispose according to local regulations)
13. Name and physical address of the manufacturer and Marketing authorization holder, if different from the Manufacturer.

    For any information about this veterinary biological product, please contact the local representative of the marketing authorization holder.
14. Date on which the package leaflet was last revised

RWANDA FDA
Rwanda Food and Drugs Authority

Certificate Nº: *RWA/FDA/DD-MA-VM/**MM-YYYY/ / APP.N^ber/Cert. Number***

MARKETING AUTHORIZATION CERTIFICATE

For

Veterinary Biological Product

Pursuant to the Law Nº. 003/2018 of 09/02/2018 establishing Rwanda Food and Drugs Authority and determining its mission, organisation and functioning, especially in its article 9 (2);

Rwanda FDA hereby issues this Marketing Authorization Certificate for the ***Veterinary Biological Product*** with details described below:

Trade/Brand Name: **[]**

Name of the Active Ingredient(s) and Strength: **[]**

Dosage form and Appearance: **[]**

Pack size: **[]**

Primary and Secondary packaging type: **[]**

Shelf life in months: **[]**

Storage Statement: **[]**

Distribution Category: **[]**

Name and address of the Marketing Authorization Holder: **[]**

Name and address of the Manufacturer: **[]**

Name of the Local Technical Representative: **[]**

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

Prof. Emile BIENVENU
Director General

Important notice

1. All changes to this product must be communicated to the Authority within the framework of the relevant provisions of the applicable guidelines;

2. This Marketing Authorization Certificate is valid for five (5) years from the date of approval unless otherwise revoked or suspended by the Authority;

3. The Marketing Authorization Holder shall ensure that the application for renewal of this marketing authorization is made 90 days before, its expiration. Otherwise, the product shall be removed from the register;

4. Registered products cannot be advertised or imported without prior approval of the Authority;

5. The product shall comply with all relevant provisions of Rwanda FDA regulations at all times;

6. The Authority reserves the right to withdraw this certificate when conditions under which it was provided for, are contravened and when the risks of using this product outweigh the benefits or it is in public interest to do so.