RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF IMMUNOLOGICAL VETERINARY PRODUCTS

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018. One of the functions of the Rwanda FDA is to regulate matters related to the quality, safety, and efficacy of Veterinary Immunological Products to protect animal health and public health in general from falsified and substandard Products.

Considering the provisions of the technical regulation No. CBD/TRG/010 of the 20th April 2020 governing the registration of medicinal products especially in its articles 1, 6, 7, 8, 9, and 32, the Authority has issued Guidelines No. DAR/GDL/066 on submission of documentation for registration of Immunological Veterinary Products on the Rwandan market.

These guidelines were elaborated to guide applicants and the Authority in managing applications for registration of immunological veterinary products using the Common Technical Document format. They were developed in reference to the East African Community's guidelines on the technical documentation required to be included in a registration dossier for an immunological veterinary product and the Tanzania guidelines on submission of documentation for registration of immunological veterinary products. In addition, various international guidelines on requirements for registration of immunological veterinary products and other relevant documents were consulted to consolidate these guidelines.

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.

24/12/2021

Dr. Emile BIENVENU
Director General

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ABBREVIATIONS AND ACRONYMS

ATCvet code	Anatomical Therapeutic Chemical code. This is a classification system for veterinary medicinal products. ATCvet is based on the same main principles as the ATC classification system for drug substances used in human medicines
EAC	East African Community
EMA	European Medicines Agency, formally known as EMEA, European Medicines Evaluation Agency
CVMP	Committee for Veterinary Medicinal Products
EPC	End of Production Cells
Hrs	Hours
INN	International Non-proprietary Name.
MCB	Master Cell Bank
MCS	Master Cell Seed
MSV	Master Seed Virus
OIE	Office International des Épizooties (International Office of Epizootics)
Ph.Eur	European Pharmacopoeia
rDNA	ribosomal DNA (Deoxyribonucleic acid); it can also mean recombinant DNA which is DNA artificially constructed by insertion of foreign DNA into the DNA of an appropriate organism so that the foreign DNA is replicated along with the host DNA
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

VICH GL	Guidelines of VICH
VICH	International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products
IVP	Immunological Veterinary Product
WCB	Working Cell Bank
WCS	Working Cell Seed
WCV	Working Cell Virus

GLOSSARY

The definitions provided below apply to the terms used in these guidelines. They may have different meanings in other contexts and documents. For these guidelines the following definitions shall apply:

Active (Immunogenic) Substance: The active substance in an immunological medicinal product, e.g. a vaccine, which is included as (one of) the antigen(s) of that formulated immunological medicinal product.

Antigen: A substance that when introduced into the body stimulates the production of an antibody. Antigens include toxins, bacteria, foreign blood cells, and the cells of transplanted organs. Where an antigen is too small to be recognized by the host it may be linked to a carrier to induce antibodies. Such small antigens are known as haptens.

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: The Rwanda Food and Drugs or its acronym "Rwanda FDA", established under Article 2 of the Law N° 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. To complete certain stages of manufacture, it may be necessary to divide a batch into several 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.

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

Finished Product: The formulated medicinal product containing the active ingredient(s) and ready for administration either alone or after reconstitution with the relevant diluents.

Immunological Veterinary Product: A veterinary medicinal product with an immunological mode of action, i.e. it induces immunity to the active substance(s) contained in a product.

Master Cell Seed (MCS): Collection of aliquots of preparation of cells, for use in the preparation of a product, distributed into containers in a single operation and processed together in such a manner as to ensure uniformity and stored in such a manner as to ensure stability.

Master Seed (MS): A collection of aliquots of preparation, for use in the preparation and testing of a product, distributed into containers in a single operation and processed together in such a manner as to ensure uniformity, and processed and stored in such a manner as to ensure stability.

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.

Seed Lot System: A system according to which successive batches of product are prepared using the same Master Cell Seed or Master Seed.

Vaccine: A preparation of weakened (attenuated) or killed pathogens, such as a bacterium or virus, or of a portion of the pathogen's structure, that stimulates immune cells to recognize and attack it, especially through the production of antibodies.

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 Seed (WCS): A collection of aliquots of preparation of cells, for use in the preparation and testing of a product, consisting of cells of a passage level intermediate between Master Cell Seed and those used for production, distributed into containers in a single operation and processed together in such a manner as to ensure uniformity, and processed and stored in such a manner as the ensure stability.

Working Seed Lot: A collection of aliquots of a preparation consisting of a passage level between Master Seed and the last passage, which forms the finished product, for use in the preparation of finished product, distributed into containers in a single operation and processed together in such a manner as to ensure uniformity, and processed and stored in such a manner as to ensure stability.

0. INTRODUCTION

0.1. Background

These guidelines were developed to guide applicants who intend to register immunological products for veterinary use in Rwanda. They were developed based on the East African Community's guideline on the technical documentation required to be included in a registration dossier for an immunological veterinary product (IVP) and the Tanzania guidelines on submission of documentation for registration of immunological veterinary products. Additionally, other relevant international guidelines and documents were consulted for guidance and consolidation of this document. The present guidelines have been prepared by taking into consideration the need for a regional and worldwide harmonization, which will assist in the preparation and assessment of a well-structured dossier to be submitted for the registration of veterinary immunological products on the Rwandan market.

This document provides details about the type of Quality information concerning the Manufacture and Control of an immunological veterinary product that the applicant should include in the registration application dossier. It also describes the data required to support the Safety and the Efficacy of the product. In addition, these guidelines describe administrative information to be included in the application dossier. The guidelines set out procedures and requirements for the application for registration of immunological veterinary products using the Common Technical Document (CTD). The CTD format has five Modules:

Module 1: Administrative Requirements

Module 2: Overview and Summaries of veterinary immunogenic substance(s) and immunological veterinary product

Module 3: Quality of the Veterinary immunogenic substance(s) and Immunological Veterinary Product

Module 4: Safety of the Veterinary immunogenic substance(s) and/or Immunological Veterinary Product

Module 5: Efficacy of veterinary immunogenic substance(s) and/or immunological veterinary product

0.2 Scope

These guidelines apply only to Immunological Veterinary Products intended for marketing in Rwanda. They describe data required to demonstrate that an Immunological Veterinary Product intended for marketing in Rwanda complies with the established requirements.

They should be read in conjunction with other international guidelines on quality, safety, and efficacy as cited in this guideline namely The World Organization for Animal Health (OIE), the European Medicines Agency (EMA), and Veterinary International Conference of Harmonization (VICH). Adherence to these guidelines by applicants will facilitate timely review and processing of product registration.

0.3 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 in these guidelines:

a) The application should be typed in English. Any document which is in any language other than English must be accompanied by a certified or notarized English translation.

b) The application must contain a complete index of the various appendices.

c) The summaries (Quality Overall Summary) should be formatted as a word document downloadable on Authority's website and the body data in PDF.

d) All pages of the application should be numbered in the style: page x of y.

e) The application should be submitted in a virus-free CD-ROM or External Driver Addressed to Rwanda FDA.

f) The PDF documents should be in Optical Character Recognition (OCR), selectable and searchable.

g) 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.

0.4 Submission of application

An application for registration of immunological veterinary products 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 local agent shall be a registered wholesale Veterinary pharmacy company or an accredited manufacturer's representative. The appointment of a Local Technical representative is certified by an appointment letter that is supported by a power of attorney notarized in the country of origin.
The application should be submitted to Rwanda FDA at the following address:
Director General
Rwanda Food and Drugs Authority
info@rwandafda.gov.rw
Nyarutarama Plaza,
KG 9 Avenue, Kigali, Rwanda

0.5 Types of Product Registration Applications

For submission of Product Dossier to Rwanda FDA, applications are classified into the following categories:

1. **New registration applications:**

An application for registration of product that is intended to be placed on the Rwandan market for the first time or product which was on the market without a registration certificate.

2. **Renewal of product registration:**

Applications for renewal of a registered product. The application shall be made at least 3 months before the expiry of existing registration according to requirements stipulated in the Rwanda FDA application guideline for renewal of the market authorization.

3. **Variation of a registered product**:

An application for any change in the registered products. All applications for variation to a registered product shall be made according to requirements stipulated in the Rwanda FDA application Guideline for Variation of Registered veterinary products.

4. Annual retention

Application for retention of registered immunological veterinary products on the register should be submitted. Applications are submitted at least 2 months before the end of each year, from the date of issuing the market authorization (MA).

Application requirements for a registered immunological veterinary product retention include:

- Application cover letter
- Proof of payment of prescribed fees (Refer to regulations related to regulatory service tariff/fees and fines: https://www.rwandafda.gov.rw/web/fileadmin/Regulation_Related_to%20Regulatory_service_tariff_fees_and_fines.pdf).

0.6 Application requirements

An application dossier for registration of IVPs in Rwanda shall include the following:

1. Signed and dated original hard copy of a cover letter
2. Signed and dated application form for product registration (*Appendix 1*)
3. Proof of payment of registration fee at the time of submission
4. Two CD-ROMs containing CTD document Format in (PDF), QOS in MS-Word
5. Two commercial samples of each pack size (The submission of samples should comply with the storage conditions as prescribed by the manufacturer to avoid any alteration of the product during transportation).
6. Proof of payment of Rwanda FDA GMP inspection for the IVP manufacturing site or GMP certificate by Rwanda FDA (if applicable)

0.7 Receiving of new applications for product registration

An application consists of electronic copies, online submission, or specified hard copies where applicable. The application of product registration is only received by the Authority when the payment of prescribed registration fees is made. After receiving a product registration application, a reference number is assigned to the application dossier submitted and it will be used in all subsequent correspondences relating to the application. An acknowledged receipt will be issued.

0.8 Officially Recognized References

The official 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 following the current edition of compendiums.

0.9 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 (OIE) and the Veterinary International Conference on Harmonization (VICH). Where specific guidelines are unavailable, Rwanda FDA adopts Committee for Medicinal Products Veterinary Use (CMPV) Guidelines, which are available at the following websites EMA: http://www.ema.europa.eu and Veterinary International Conference on Harmonization (VICH) Guidelines: https://www.vichsec.org/en/

0.10 Rwanda FDA Dossier Assessment Procedures

0.10.1 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) rules. Priority assessment may be granted where the product is intended for the control of rare disease conditions through an expression of interest (EOI DHT/FMT/032) or in the case of an emergency situation.

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 an immunological veterinary product. During the assessment, additional data and/or samples may be requested through an official communication letter. Once a query has been issued to the applicant, the assessment process stops until Rwanda FDA receives a written response to the raised queries. Further processing of the application may only be undertaken if responses to queries issued in the official communication letter contain all outstanding information requested in one submission. Failure to comply with this condition or if the queries have been reissued for the fourth time and the applicant provides unsatisfactory responses, the application will be rejected.

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

0.10.2 Rwanda FDA Peer Review Committee for Product Registration

After Dossier Assessment Workshop, a final dossier assessment report shall be presented to Rwanda FDA Peer Review Committee (PRC) before making final decisions for granting or rejecting market authorization of the product.

In the event, that there are safety, quality, or efficacy issues to be resolved as per the decision of the PRC, the application shall remain pending until the resolution of the raised issues.

Rwanda FDA will register the product which data on safety, quality, and efficacy are considered satisfactory and a registration certificate of Immunological veterinary products *(Appendix 2)* will be granted. The registration shall be valid for five (5) years with annual retention. If Rwanda FDA suspends or cancels the registration validity, a written official communication shall be made to the applicant.

0.11 Compliance with 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 GMPs issues and communicate to the department that has the mandate of inspection and compliance. More information on GMP 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 No DIS/GDL/002 and its annexes No DIS/GDL/003) downloadable from Rwanda FDA website.

0.12 Timeline 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 nine (9) months of receipt of the application. The applicant will be required to provide any requested additional data within ninety (90) calendar days. Additional data or query responses shall be processed within sixty (60) calendar days.

MODULE 1: ADMINISTRATIVE INFORMATION

Module 1 should contain all administrative documents such as the duly completed application form, certifications, letters, Licenses, reports, annexes among others, as needed. Documents submitted in module one can be submitted as separate files or in one file. All applications and supporting documents should be in English. Documents should be organized in the order listed below:

1.1 Comprehensive Table of Contents for all Modules

The table of contents should indicate the sections, subsections, and corresponding page numbers for the entire application.

1.2 Application Letter

An application letter should be submitted with the product dossier clearly indicating the product seeking a market authorization, the applicant, the contact details (telephone number, e-mail, and fax) of the applicant, and the submitted documents (CDs, Samples, etc.). The letter should be signed by the Applicant.

1.3 -Application form

An application for registration of immunological veterinary products on the Rwandan market must be accompanied by a duly completed application form (Appendix 1). 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 immunogenic 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 immunogenic substance(s) manufacturer (s) should be provided.

1.5 Mock-Ups

Mock-ups of the sample(s) presentation of the immunological veterinary 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 (SmPCs)

All applications for registration of immunological veterinary products should be accompanied by a summary of product characteristics (SmPCs) or prescribing information. The SmPCs 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 following the consent of the applicant.

1.7 Container Labeling

Containers should be labeled as recommended in *Appendix 4* of these guidelines. This should be provided as mock-ups

1.8 Product Information Leaflet (PIL)

Every container of Immunological Veterinary 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.

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 immunological product, active substance(s), the diluents, and those responsible for labeling and packaging of the finished immunogenic product.
In addition, a copy of a GMP certificate issued by Rwanda FDA or proof of application (such as a proof of payment), to GMP inspection of the finished immunogenic 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 authorized by Rwanda FDA to deal in veterinary 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.

MODULE 2: OVERVIEWS AND SUMMARIES

The purpose of this module is to summarize the quality, safety, and efficacy information presented in modules 3, 4, and 5 in the market authorization application. The information in module 2 should be presented in world format in the following order:

2.1 Table of contents of Module 2

A table of content of module 2 should be provided.

2.2 CTD Introduction

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

2.3 Quality Overall Summary (QOS)

The Quality Overall Summary is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data, or justification that was not already included in Module 3 or other parts of the CTD. The QOS template is in *Appendix 6* of this guideline. The QOS should be provided in a word version.

2.4 Summary of safety data

All the data related to safety assessed through the development of the product, as well as any study limitations, should be summarized and presented in this section. Summaries should include all the laboratory and field studies performed and a synopsis of each study.

2.5 Summary of efficacy data

All the data related to efficacy assessed through the development of the product, as well as any study limitations, should be summarized and presented in this section. Summaries should include all the laboratory and field studies performed and a synopsis of each study.

MODULE 3: QUALITY INFORMATION

3.1. Table of Contents of Quality Part

A table of content of the filed product dossier should be provided

3.2. Body data

3.2.S Immunogenic substance(s)

The information requested under this section should be supplied individually for each immunological substance in the product and should be completed for each immunogenic substance identified as being present in the final immunogenic product.

3.2.S.1. General information

3.2.S.1.1 Nomenclature

Description of Immunogenic Substance; provide a clear description of the immunogenic substance. The biological name (including strain and/ or clone designation) or chemical name,

including any approved name, should be provided. The name(s) or designation of the strain of organism used to produce the active immunogenic substance should be provided. The description should also include the source of the cells, including microbes from which the immunogenic substance was derived, the active components of the cell fractions or purified antigens, and the physical and chemical properties of the synthetic immunogenic substance.

Any chemical modification or conjugation of the immunogenic substance should be described in detail. Also, a list of any inactive substance, which may be present in the immunogenic substance, should be provided.

3.2.S.1.2 Structure

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

3.2.S.1.3 General Properties

A list of physicochemical and other relevant properties of the immunogenic substance, including biological activity, should be provided. The description of a rDNA- derived biotherapeutics should indicate the biological system in which it is reduced (e.g. bacterial, fungal, or mammalian cells) as well as the presentation of the finished product.

3.2.S.2. Manufacturing Process for The Immunogenic Substance(s)

3.2.S.2.1 Manufacturer(s)

The name(s) and physical address (es) of the manufacturer(s) of the immunogenic substance including activities performed at each manufacturing site should be provided.
The facilities involved in the manufacturing, packaging, labeling, testing and storage of the active substance should be listed. The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and units(s). Telephone number(s), fax number(s), and e-mail address (es) should also be provided.

A valid certificate of GMP compliance should be provided for the active immunogenic substance. If available, a manufacturing authorization should be provided in Module 1.

3.2.S.2.2 Method of Manufacture

3.2.S.2.2.1 Flow chart of the manufacturing process

A complete visual representation of the manufacturing process flow should be provided for each active immunogenic substance. Steps in production, including incubation times and temperatures, equipment and materials used, the area where the operation is performed, and a list of the in-process controls and finished product tests performed at each step should be clearly shown. In-process holding steps should be included with time and temperature limits indicated.

3.2.S.2.2.2 Description of Manufacturing Process

A detailed description of each process step as presented in the flow chart substance should be provided.
A description of manufacturing starting with the Master Seed and procedures used to derive a Working Seed from the Master Seed should be provided. Media and the identification system used for the working Seed Bulk (WSB), as well as the procedures for storage and cataloging of the WSB and any steps in which the bulk of the active immunogenic substance is further processed (e.g separated from the cells, concentrated), should be provided. A list of all the components used in the manufacturing process including media, solvents, or solutions should also be provided.

A description should be provided for:

1. Propagation and Harvest

For each Immunological substance/ antigen production method or combination of methods, a growth curve or tabular representation of growth characteristics for each propagation step should be provided. A table showing the yield, purity, and viability (if applicable) of the crude harvest should also be included.

2. Inactivation (if appropriate)

Inactivation kinetics or killing curves, or a tabular representation should be provided. Validation of the titration method used to measure residual live organisms, including the sensitivity of the method in a background of inactivating agents, should be provided. The following information should be provided:

- How Culture purity is verified before inactivation.

- The method(s) and agent(s) used for inactivation.
- The method(s) undertaken to prevent aggregation and assure homogeneous access of inactivating agent(s) to the culture.
- The stage in production where inactivation or killing is performed
- The parameters which are monitored.

3. Detoxification (if appropriate)

For toxoid or toxoid-containing vaccines, the detoxification procedures should be described in detail for the toxin component(s):

- The method(s) and agent(s) used for detoxification
- The stage in production where detoxification is performed and the parameters, which are monitored, must be described.

4. Purification (if appropriate)

Describe any purification methods used, including specialized equipment such as columns, ultracentrifugation, ultra-filtration, and custom reagents such as monoclonal antibodies. The process parameters monitored and the process for determination of yields should be stated.

For each purification method or combination of methods used, a tabulation of yields, purity and biological activity should be provided. Verification of the removal or dilution of product-related and non-product related impurities, e.g. processing reagents, endotoxin contaminating cell proteins or nucleic acids, and other residual contaminants should be included. A standard denominator (e.g. international units) should be used to facilitate comparison through processing, concentration, or dilution. If the purified substance is held prior to further processing, a description of the storage conditions and time limits should be included.

5. Stabilization process (if applicable)

A description should be provided for any post-purification steps performed to produce a stabilized immunogenic substance (e.g. adsorption, the addition of stabilizers, the addition of preservatives), and the objectives and rationale for performing each process.

A description of precautions taken to monitor bio-burden and prevent contamination during these processes should also be provided. If the substance is held prior to further processing, a description of storage conditions and time limits should be included. Verification of the stability of the active immunogenic substance under the conditions described should be provided.

6. Provide the criteria for pooling more than one batch (if applicable)

The details on reuse and/or regeneration of columns and adsorbents and monitoring for residual impurities and leachable reagents should be provided.
Depending on the source of the immunogenic substance, other details about the manufacturing process are provided in *Appendix 7*.

3.2.S.3. Manufacturing Consistency

Consistency of the manufacturing process for each immunogenic substance component should be demonstrated by providing the manufacturing lot certificates of at least three, preferably consecutive, batches of the active immunogenic substance of a size corresponding to that for routine production. The establishment and use of the reference standards in assuring consistency in product characteristics.

3.2.S.4. Reference standards or materials

The establishment and use of reference standards or materials in assuring consistency in product characteristics should be described. Information under this section should include a description of the preparation, characterization, and stability of primary and working reference standards. A detailed description of the procedures to qualify new lots of reference standards and acceptance criteria for a new reference standard should be included. Certificate(s) of analysis of reference standard or materials used should also be provided.

3.2.S.5. Container and Closure System

A description of the container and closure system and information on its compatibility with the immunogenic substance should be provided. Detailed information concerning the supplier, address, and the results of compatibility, toxicity, and biological tests should be included. If the immunogenic substance is intended to be sterile, evidence of container and closure integrity for the duration of the proposed shelf life should be provided.

3.2.S.6. Stability of immunogenic substance

This section should contain information on the stability of the immunogenic substance and any in-process material at each holding step. At least stability data from three consecutive batches should be provided.

3.2.S.6.1 Protocol of stability study, summary, and conclusions

The stability protocol which includes all the storage conditions (temperature, humidity, light) in which the immunogenic substance is evaluated should be provided.

3.2.S.6.2 Stability data

Stability data should be provided for at least three representative consecutive batches stored in the final container.

3.2.S.6.3 Storage and shipping conditions of immunogenic substance

When applicable, the equipment used, areas, buildings (if pertinent), the shipping, and storage conditions should be described.

3.2.P Immunological Veterinary Product (IVP)

3.2.P.1.Description and Composition of the IVP

Information provided should include

3.2.P.1.1 Description of the dosage form

In this section, a clear description of the IVP and packaging materials should be provided.

3.2.P.1.2 Qualitative and Quantitative Particulars

A tabulated list of all components of the immunological veterinary product and diluents (if applicable) should be given as per table 1 below. The quantities per dose should be stated. A clear description of the active immunogenic substance including the name(s) or designation of the strain of organism used to produce the active immunogenic substance should be provided. The reason(s) for the inclusion of each excipient, reference standard, and a justification for overages should also be stated. Where applicable, special characteristics of excipients should be indicated. The type of water (e.g. purified, demineralized), where relevant, should be indicated.

Table 1: Composition of the Immunological Veterinary Product

1. Active (immunogenic) ingredients

Name	Function/reason for inclusion	Quantity per dosage Unit	Specification or reference text

2. Inactive ingredients (adjuvant/excipients/preservative)

Name	Function/reason for inclusion	Quantity per dosage Unit	Specification or reference text

3.2.P.2. Method of manufacture

3.2.P.2.1 Manufacturer

The name(s) and physical address (es) of the manufacturer(s) of the IVP including activities performed at each manufacturing site including contract manufacturers for production and quality control should be stated. The manufacturing authorization and certificates of compliance with GMP requirements should be provided in module 1.

3.2.P.2.2 Flow chart of the manufacturing process

A complete visual representation of the manufacturing process flow should be provided for the immunological veterinary product. The steps in production, including incubation times and temperatures, equipment and materials used, the areas where the operations are performed and a list of the in-process controls and finished product tests performed at each step should be stated. In-process holding steps should be included with time and temperature limits indicated.

3.2.P.2.3 Description of the manufacturing process

A detailed description of the manufacturing process of the IVP including the sterilization operations, aseptic processing procedures, filling, lyophilization (if applicable), and packaging should be provided. Results of studies validating the compatibility of the components including the adjuvant and/or preservatives, if applicable, should be provided.

3.2.P.2.4 Control of Starting Materials

A list of all starting materials including culture media, buffers, and resins for peptide synthesis, chemicals used in the manufacture of the immunogenic substance, and their specifications or reference to official compendia should be provided. For purchased starting materials, representative certificates of analysis from the supplier(s) and/or manufacturer's acceptance criteria should be provided. Monographs of starting materials listed in pharmacopeias and starting materials not listed in a pharmacopeia (description and seed materials for starting materials of biological origin, and description and identification of starting material of non-biological origin).

In-house preparation of media should be described.

1. Starting material listed in pharmacopeias
2. Starting materials not listed in pharmacopeias
   - 2.1. Starting materials of non-biological origin
   - 2.2. Starting materials of biological origin

     Details on the control of starting materials of biological origin are provided in *Appendix 8*.

3.2.P.2.5 Minimising the risk of TSE

The carry-over of impurities of the starting materials for synthesis into the final immunogenic substance should be considered and discussed.

A letter of attestation should be provided confirming that the active substance, the starting materials, and reagents used to manufacture the immunogenic substance are without risk of transmitting agents of animal spongiform encephalopathies. When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module1.

3.2.P.2.6 Media preparation

Details of methods of preparation and sterilization of all media must be provided. Culture media must be stored at the specified temperature, under specified conditions, and for no longer than the applicable shelf life. Quality control tests should be carried out to ensure that the performance characteristics of the medium are within specification.

3.2.P.2.7 In-process control tests

A description of all analytical testing performed to characterize the active immunogenic substance with respect to identity, quantity, and stability with their test results should be presented in either tabular form, legible copies of chromatograms or spectra, photographs of gels or immunoblots, actual histograms of cytometric analysis or other appropriate formats. The report should also include a brief description of sampling procedures and test methods. Data should be well organized and fully indexed to enable easy access. Results for quantitative assays should be presented as actual data not generally as "Pass" or "Fail".

- Control of Bio-burden

For any process, which is not intended to be sterile, documentation of the control of extraneous bioburden by a tabulation of in- process testing for bioburden should be provided.

3.2.P.2.8 Process Validation

A complete report, including protocols, results, and control standards used should be provided for the validation studies of each critical process or factor that affects active immunogenic substance specifications. The validation study reports that have been subjected to statistical rigor should demonstrate the variability in each process as it relates to final specifications and quality. The characteristics of specific antibodies used in the immunochemical or serological assays should also be included.

3.2.P.3 Control Tests on the Finished Product

3.2.P.3.1 Specifications

Detailed information on finished product tests performed on each batch, including the batch release specification, must be provided. The following information should be provided:

a. Appearance

A qualitative statement describing the physical state (lyophilized solid, powder, liquid) and color and clarity of the Immunological Veterinary Product.

b. Identity

The method used to establish the identity of the IVP, including the identification of the active substance(s) should be described. The description should include an evaluation of the specificity and sensitivity of the method.

c. Purity/sterility

Include information on the purity or sterility of the Immunological Veterinary Product.

d. Safety

If available, Provide results of the batch safety tests performed in the target animal species. (EMA reference) If available

e. Potency/Titer

A description of the potency assay for the Immunological Veterinary Product should be provided. Information should be submitted on the sensitivity, specificity, and variability of the assay including the data from the material used to prepare clinical lots which were used to set the acceptance limits for the assay.

f. Chemical and Physical tests

Provide information on the chemical and physical tests carried out on the finished Immunological veterinary product. These shall include: pH and, if applicable, adjuvant, preservative, residual humidity, viscosity, emulsion, residual inactivate, etc.

g. Sampling procedures

The sampling procedures for monitoring a batch of an immunological veterinary product should be included.

3.2.P.3.2 Analytical methods

A description of all test methods selected to assure the identity, purity, titer/or potency, as well as the lot-to-lot consistency of the finished product and the specifications used for the immunogenic product should be submitted.

3.2.P.3.3 Validation of analytical methods

The results of studies validating the specificity, sensitivity, and variability of each method used for release testing should be provided. Where applicable this should include descriptions of reference standards and their validation. For analytical methods in compendial sources, the appropriate citations should be provided.

3.2.P.4 Batch to batch consistency

Provide at least three consecutive production batches of the immunological veterinary product of a size corresponding to that for routine production. Results from the three consecutive batches should be provided in tabular form for ease of comparison. Certificates of analysis of each batch should be provided. The manufacturing records of these three batches should be provided.

3.2.P.5 Containers

Details of the container and closure system and its compatibility with the immunological veterinary product should be submitted. Detailed information concerning the supplier(s), address (es), and the results of any relevant information on compatibility, toxicity, and biological tests should also be provided for containers of novel origin.

For sterile products, evidence of container and closure integrity should be provided for the duration of the proposed shelf life.
Container closure system - specifications including descriptions and identification of primary packaging components should be provided.

3.2.P.6 Stability of the Final Immunological Veterinary Product

Evidence should be provided to demonstrate that the product is stable for the proposed shelf-life period under the storage conditions described on the label. The ultimate proposed shelf life should be stated.

3.2.P.6.1 Protocol of stability study, summary, and conclusions:

Stability protocol and data should be provided for at least three representative consecutive batches stored in the final container. The three consecutive production runs may be carried out on a pilot scale (10% of full scale), providing this mimics the full-scale production method described in the application, or manufacturing scale (the largest scale validated and proposed for registration for commercial use). The storage temperature should be stated together with the results of tests on the

batches. A plan for on-going stability studies should be provided indicating the batch numbers of the batches on test and the time points when testing is planned.

Examples of stability-indicating tests to be performed:

a. Sterility at time zero and end of shelf life
b. Potency/virus titer/bacterial counts
c. Physical and chemical tests, as appropriate, such as:

   - Moisture content of lyophilized vaccines (VICH GL26).
   - Tests to quantify the adjuvant.
   - Oil adjuvanted vaccine should be tested for viscosity by a suitable method.
   - The stability of the emulsion should be demonstrated.
   - Quantitative assay of any preservatives. For multi-dose presentations, when a preservative is included in the vaccine, preservative efficacy should also be studied at the minimum and maximum time points as defined in Ph. Eur.5.1.3 and at the lower preservative limit at the end of shelf-life specification if there is a range.
     Note: A preservative may only be included in a single dose vial if it can be shown that the single-dose vial is filled from the same bulk blended vaccine as a multi-dose container.
     The pH of liquid products and diluents should be measured and shown to be within the limits set for the product.

d. Target animal safety testing: for conventional vaccines, it may be acceptable to omit the target animal safety test at each shelf life testing point.

The shelf life starts at the time of the first titration (live vaccines) or potency test. For example, for in vivo potency tests, the shelf life starts from the date of the first administration of the vaccine to the species in which the potency test is carried out.

For vaccines stored by the manufacturer at a temperature lower than that stated on the label, the stability for the entire storage period should be demonstrated. The expiry date is then calculated from the date that the vaccine is stored under the conditions stated on the label.

3.2.P.6.2 In-use shelf life

Stability-indicating tests should be provided on at least 2 different batches to support an in-use shelf life. Target animal safety testing is not normally required.

1. After first opening the container

Generally, an in-use shelf life after the first opening should not exceed 8-10 hrs.
For live vaccines an in-use shelf life of 8-10 hours must be supported by virus/bacterial titration data. For inactivated vaccines omission of the potency test at the end of the in-use shelf life can be justified if the potency test is an in-vivo test.

2. Shelf-life after dilution or reconstitution

The shelf life after reconstitution according to the directions should not exceed 10 hours. The product must be reconstituted with the approved diluents and in line with the recommendations. The shelf life after reconstitution must be supported by virus/bacterial titration or potency data. No losses of titer or potency should be observed. For inactivated vaccines omission of the potency test at the end of the in- use shelf life can be justified if the potency test is an in-vivo test.

3. Extended in-use shelf life:

A CMPV guideline (EMEA/CVMP/IWP/250147/2008) on data requirements to support in-use stability claims for veterinary vaccines is available. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-data-requirements-support-use-stability-claims-veterinary-vaccines_en.pdf. The guideline places emphasis on conducting the in-use stability study mimicking the conditions of use of the vaccine in the field.

Note: For guidance on "Stability testing of Biotechnological Veterinary Medicinal Products" refer to VICH GL 17 (CVMP/VICH/501/99) found at https://www.ema.europa.eu/en/documents/scientific-guideline/vich-gl17-stability-testing-biotechnological/biological-veterinary-medicinal-products-step-7_en.pdf

3.2.P.6.3 Description of procedures to guarantee cold chain

Describe in detail the measures used to guarantee adequate temperature and humidity conditions for shipping the finished 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.

3.2.D Manufacturing and controls of Reconstitution diluents

For any immunological veterinary product accompanied with reconstitution diluents, the following data should be submitted for diluents(s):

a. Name of reconstitution diluents(s)
b. Name and physical address of the manufacturer, telephone, and e-mail of the reconstitution diluents(s)

c. Valid Certificate of Good Manufacturing Practice and Valid Manufacturing Authorization for the production of the diluent(s) should be provided in module 1.)
d. Description of the reconstitution diluents(s)
e. Qualitative and Quantitative particulars

A tabulated list of all components of the diluents (if applicable) should be given as per table 4 below. Name of diluents, Quantity per dosage unit, and the reason(s) for inclusion of each excipient (if applicable) should be stated.

Name	**Quantity per Unit dosage**	**Quantity per batch**	**Specifications/ Reference text**	**Reasons for inclusion**

f. Specification of reconstitution diluents(s) along with certificates of analysis
g. Description of manufacturing method production and control of starting materials
h. Control tests during the manufacturing process
i. Compatibility studies with reconstitution diluents to support claims in the label. The compatibility of diluents e.g. precipitation of IVP in solution, sorption on injection vessels, and stability should be addressed to provide appropriate and supportive information for labeling.
j. Process validation report
k. Control tests of the finished product
l. Sterility tests
m. Analytical validation report
n. Specifications of container closure system along with certificates of analysis
o. Stability report that includes:
   - The study protocol,
   - Specifications,
   - Analytical method,
   - Description of the container closure system for the diluents,
   - Storage conditions (temperature and relative humidity),
   - Summary of results for at least three batches of diluents
   - Proposed validity period
   - The stability documents should be provided on an officially recognized document, signed by responsible personnel, dated with a version control number.

MODULE 4: SAFETY

4.1 Table of contents of Module 4

4.2 Report on studies

Reports of laboratory tests and field trials performed to demonstrate all aspects of safety of the product during use, together with the conclusions, should be provided.
The reports relating to the laboratory tests and field trials should be written using the sequence of headings below:

a. Title of the test, with reference number
b. Introduction including a statement of the aims of the test study
c. Reference to relevant monographs
d. Name(s) and business address (es) of key personnel and location of the research institute involved in the study
e. Dates of start and end of the test or study
f. Summary
g. Material and methods
h. Results
i. Discussion
j. Conclusion

4.2.1.Laboratory Tests

For guidance on how to design and monitor these studies refer to CVMP/VICH/359665/2005, VICH GL44: "Target animal safety for veterinary live and inactivated vaccines". https://www.ema.europa.eu/en/documents/scientific-guideline/vich-gl44-target-animal-safety-veterinary-live-inactived-vaccines-step-7_en.pdf

4.2.1.1.Single-dose toxicity studies

The immunological veterinary product should be administered at the recommended dosage and by the recommended route of administration to each species in which it is intended to be used. The animals should be monitored daily for 14 days, observing and recording objective criteria such as rectal temperature, injection site reaction, and effect on performance.

4.2.1.2.Overdose toxicity studies

The immunological veterinary product should be administered at an overdose (normally 10 times the recommended dose for live vaccines and 2 times for inactivated vaccines) by the recommended route of administration to each species in which it is intended to be used. The animals should be monitored daily for 14 days, observing and recording objective criteria such as rectal temperature, injection site reaction, and effect on performance.

4.2.1.3.Repeated dose toxicity studies

The immunological veterinary product should be shown to be safe by considering the number of doses that are likely to be used by the animal during its lifetime. For example, if the vaccination schedule requires a 2-dose primary course followed by a single annual booster, the repeated administration test should consist of 3 separate doses. The doses may be given 2 weeks apart by the recommended route of administration to each species in which it is intended to be used. This study may be run in conjunction with the single-dose study.
The animals should be monitored daily for 14 days after each administration, observing and recording objective criteria such as rectal temperature, injection site reaction, and effect on performance.

4.2.2. Safety studies for live attenuated vaccines

a. Spread of the vaccine strain

Shedding and spread of the vaccine strain from vaccinated to unvaccinated animals should be studied and assess the implications of the results should be reported.

b. Dissemination in the vaccinated animal

Studies to demonstrate if the vaccine strain is present in animal secretions or the tissues of the vaccinated animal should be conducted.

c. Safety of a live, attenuated vaccine from Reversion to Virulence

These studies should be conducted according to the following guidance CVMP/VICH/1052/2004, VICH GL41: "Target animal safety: Examination of live veterinary vaccines in target animals for the absence of reversion to virulence."

https://www.ema.europa.eu/en/documents/scientific-guideline/vich-gl41-target-animal-safety-examination-live-veterinary-vaccines-target-animals-absence-reversion_en.pdf

d. Recombination or genomic re-assortment of strains

Discussion should be provided on the probability of recombination or genomic re- assortment with field or other strains.

4.2.3. Field Safety

The safety of the immunological veterinary product should be evaluated during field trials. Both safety and efficacy may be assessed during the same trial. Batches used in the trials must be manufactured according to the method described in Module 3.

4.2.4. Other Safety Issues to be considered

1. Safety to the user

   For specific guidance on safety to the user reference should be made to CVMP/54533/06, adopted guideline: "User safety for immunological veterinary products".

2. Safety to the environment

   For specific guidance on safety to the environment, reference should be made to CVMP/074/95 "Environmental risk assessment for immunological veterinary products".

3. Safety of residues

   For food-producing animals, the effects of residues of constituents of the vaccine such as adjuvants or live zoonotic organisms used as antigens should be considered. A suitable withdrawal period should be provided.

4. Interactions

   The safety of administering the immunological veterinary product at the same time or the same site as another immunological veterinary medicinal product must be demonstrated if a recommendation for such use is to be made on the SmPC.
   For specific guidance on the safety for combined vaccines and associations of immunological veterinary medicinal products reference should be made to CVMP/IWP/594618/2010,

"Requirements for combined vaccines and associations of immunological veterinary medicinal products (IVMPs)".

MODULE 5: EFFICACY

5.1. Table of contents for Module

5.2. Efficacy studies Reports

Particular tests in the target species of animal to demonstrate the efficacy of the IVP to support the indications for which it will be used should be provided. Details of the following studies should be provided.

5.2.1. Laboratory Efficacy

5.2.1.1. Controlled clinical studies on efficacy (Immunological Veterinary Products-challenge studies)

Evidence of efficacy under reproducible controlled conditions should be provided. Efficacy should normally be demonstrated by administering a challenge infection with a heterologous strain. If protection against challenge infection has been shown to correlate with serology it may be possible to demonstrate efficacy by serological methods. The batch (es) used in laboratory efficacy studies should be manufactured and tested according to the methods described in Module 3 and contain the minimum quantity of antigen permitted for batch release. It should be administered to the target species at the recommended dose by the recommended route of administration.

5.2.1.2. Compatibility studies

Where relevant data should be provided on the following studies:

a. Studies on potential beneficial interactions with other IVP administered at the same time.

b. Studies on the potential decrease in efficacy when administered at the same time as other IVP (interference).

Each individual study report should include the following information:

a. Identity and qualifications of key personnel involved

b. Location(s) of study
c. Date(s) of study
d. Study design
e. Selection of animals (inclusion, exclusion criteria)
f. Selection of controls
g. Selection of control treatment (if applicable)
h. Number of animals involved.
i. Response variables – endpoints
j. Details on – randomization, blinding, compliance, and justification.
k. Treatments given – identity and quality of the investigational and control products used, the dosage used, duration of treatment, duration of observation periods, any concurrent treatments, and their justification
l. Analytical methods for determining antibodies if serology is applicable as a measure of efficacy
m. Analysis of results including statistical analysis
n. The proposed indication(s) of the product should be stated.
o. Discussions and conclusions on efficacy and safety

5.2.2. Field Efficacy

The immunological veterinary product should be tested in controlled field trials. The batch (es) used in field trials should be manufactured and tested according to the methods described in module 3. It should be administered to the target species at the recommended dose by the recommended route of administration. For specific guidance on conducting field efficacy trials reference should be made to EMA/CVMP/852/99, "Field trials with veterinary vaccines".

ENDORSEMENT OF THE GUIDELINES

	Author	Authorized	Approved
Title	DM/Veterinary Medicine Devices Assessment and Registration Division	Head of Drug&Food Assessment and registration Department	Director General
Names	Dr. Manishimwe Rosine	Kabatende Joseph	Dr. Bienvenu Emile
Signature			
Date	22/12/2021	22/12/2021	24/12/2021

ANNEXES

Appendix 1. APPLICATION FORM

Rwanda Food and Drugs Authority
Nyarutarama Plaza, Rwanda
KG 9 Avenue, Kigali
P.O. Box 1948, Kigali, Rwanda
E-mail: info@rwandafda.gov.rw
Website: www.rwandafda.gov.rw

QMS N°: DAR /FOM/154
Rev. N°: 0
Effective date: 27/12/2021
Revision due date: 27/12/2024

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 the 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.

3.2 Therapeutic Subgroup Classification *(example, inactivated viral vaccine, diuretic drug)* and ATC Code (if applicable)

3.3 Dosage Form and Strength *(example, solution for injection)*

3.4 Visual appearance *including colour (example, clear, light yellow oily solution)*

3.5 Target Species and Route(s) of Administration

	Target Species	Route of Administration	Food-producing? (tick as appropriate)
1			Yes ☐ No ☐
2			Yes ☐ No ☐

Please add extra rows, if required.

3.6 Do all active substances have the appropriate Maximum Residue Limits (MRLs) set in the species and for the route of administration(s) for which they are indicated? For example, from Codex, EU or other.

YES ☐ NO ☐

If yes, states the MRLS

Target Species	Tissue	MRLs	Reference (Codex, EU,…)

If no, please tell us what you are doing to obtain the appropriate MRL(s):

3.7 Pack type details

Please provide information of all pack types including their container and closures.

	Pack Size *(example, 100 ml)*	**Container** *(example HDPE bottle)*	**Closure** *(example, polyethylene screw-cap)*
1			
2			

Please add extra rows, if required.

3.8 Proposed shelf-life (if applicable also include the proposed shelf life after reconstitution or dilution or after first opening container)

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/authorisations 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

Appendix 2. REGISTRATION CERTIFICATE OF IMMUNOLOGICAL VETERINARY PRODUCT

DAR/FMT/131

RWANDA FDA
Rwanda Food and Drugs Authority

REGISTRATION CERTIFICATE OF IMMUNOLOGICAL VETERINARY PRODUCT

Made under Law No. 003/2018 of 09/02/2018 establishing the Rwanda FDA and determining its mission, organization and functioning in his article 3 and article 8 and regulation No. CBD/TRG/010. The Authority here issues

Registration number: Rwanda FDA-IVP-MA-000 ******

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

Brand Name: ******

Name of the Active immunogenic ingredient(s) and Strength: ******

Indication: ******

Dosage Form and appearance: ******

Pack size and Packaging type: ******

Shelf life in months and Storage statement: ******

Distribution category: ******

Name of Marketing Authorization Holder: ******

Name and address of manufacturer: ******

Name of Local Technical Representative: ******

Issued on: ******

Expires on: ******

Dr. Emile BIENVENU
Director General

Conditions for Immunological Veterinary Product Registration

1. This certificate must be returned to the Authority if canceled, invalidated or if the registered Immunological Veterinary Product is withdrawn.
2. Any change in the information submitted for the purpose of registration must be notified to the Rwanda FDA within 30 days of the change.
3. 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.
4. Registered Immunological Veterinary Product cannot be advertised without prior approval of the Authority.
5. The Immunological Veterinary Product shall comply with all relevant provisions of Rwanda FDA regulations at all times.
6. The Marketing Authorization Holder shall ensure that registered Immunological Veterinary Product complies with Rwandan labelling and packaging requirements at all times.
7. The Marketing Authorization Holder shall ensure that the manufacturing facilities where a registered Immunological Veterinary Product is produced comply at all times with Rwanda FDA Good Manufacturing Practice requirements.
8. The Marketing Authorization Holder shall notify Rwanda FDA of the change of a Local Technical Representative at all times.
9. The registration of the Immunological Veterinary Product shall continue to be valid for five (5) years provided that annual retention fee is paid.
10. The Authority reserves the right to withdrawal this certificate when conditions 1 to 7 are contravened and when the risks of using this Immunological Veterinary Product outweighs the benefits or it is in public interest to do so.

Appendix 3. SUMMARY OF PRODUCT CHARACTERISTICS (SmPC) FOR AN IMMUNOLOGICAL VETERINARY PRODUCT

1. Name of the immunological veterinary 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 immunogenic 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. Immunological dosage form

State clearly the immunological dosage form of the product. Any descriptive terms to indicate 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, state whether for active or passive immunity. Give information on the onset and duration of immunity. See also CMPV "Position Paper on Indications and Specific Claims for Immunological Veterinary Products" ref.: CVMP/IWP/042/97- Rev.1, 2003, and SPC Guideline.

4.3. Contraindications

State the contraindications for this immunological veterinary 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 immunological veterinary product (if any). State the precautions that should be taken for use in animals.

4.6. Adverse effects following immunization (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. Information on the reasons for the relevant recommendation should be given. In the absence of data, the use of this vaccine is not recommended.

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

State briefly the interactions of the product with other types of medicinal products, or state whether compatible with other immunological 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. A distinction should be made between the primary vaccination course and any booster doses.

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. Immunological properties

State the immunological properties of the product e.g. to induce active immunity, or to provide passive immunity.

6. Immunological veterinary product particulars

6.1. Incompatibilities

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

6.2. Shelf life

- Shelf life (in months) of the immunological veterinary product.
- State the immunological veterinary product 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 medicinal product and waste materials derived from the used/unused vaccines (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.

Appendix 4. CONTAINER LABELING

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

PARTICULARS TO APPEAR ON THE PRIMARY PACKAGE

1. Name of the immunological veterinary 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 immunological veterinary 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 IVP.
2. Name of the manufacturer.
3. The batch number assigned by the manufacturer.
4. The manufacturing and expiry dates.

<u>Appendix 5.</u> PRODUCT INFORMATION LEAFLET (PIL)

PARTICULARS TO APPEAR ON THE PACKAGE LEAFLET

1. Name of the immunological veterinary product
2. Name and quantity of active substance(s) and excipients
3. Indication(s)
4. Contraindications, warnings and precautions
5. Adverse effects following immunization (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 medicinal product, please contact the local representative of the marketing authorization holder.
14. Date on which the package leaflet was last revised

Appendix 6. QUALITY OVERALL SUMMARY (QOS) FOR IMMUNOLOGICAL VETERINARY PRODUCTS

Rwanda Food and Drugs Authority
Nyarutarama Plaza, Rwanda
KG 9 Avenue, Kigali
P.O. Box 1948, Kigali, Rwanda
E-mail: info@rwandafda.gov.rw
Website: www.rwandafda.gov.rw

QMS N°: DAR /FOM/155
Rev. N°: 0
Effective date: 27/12/2021
Revision due date: 27/12/2024

Quality Overall Summary (QOS) for Immunological Veterinary Products

GENERAL INSTRUCTIONS

Quality overall summary (QOS) template should be completed for immunological veterinary product (IVP) containing active immunogenic 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 "Guideline on submission of documentation for registration of immunological veterinary product (IVP) 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 IMMUNOGENIC 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 of the immunogenic substance

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 Method of manufacture

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

S.3. Manufacturing Consistency

Consistency of the manufacturing process for each immunogenic substance component should be demonstrated by providing the manufacturing lot certificates of at least three, preferably

consecutive, batches of the active immunogenic substance of a size corresponding to that for routine production.

2.3. S.4 Reference Standards or Materials (name, manufacturer)

Source (including lot number) of primary reference standards or reference materials (e.g.Ph.Int., Ph.Eur., BP, USP, in-house). 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). Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against a primary standard).

2.3. S.5 Container closure system of the immunogenic substance

A brief description of the container and closure system and information on its compatibility with the immunogenic substance.

2.3. S.6 Stability of the immunogenic substance

1. Stability Studies Protocol, summary, and conclusions
2. Stability data
3. Proposed storage and transportation conditions

2.3. P FINISHED IMMUNOGENIC PRODUCT (NAME, MANUFACTURER)

2.3.P.1 Description and Composition

- Description of the finished immunogenic product.
- Composition of the finished immunogenic 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							

Type of container closure system used for the IVP and accompanying reconstitution diluents, if applicable.

2.3. P.2 Method of manufacture of the finished immunogenic product

2.3.P.2.1 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.2.2 Manufacture Flow Chart

Flow diagram of the manufacturing process

2.3.P.2.3 Manufacture process details

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

2.3.P.2.4 Control of starting materials

3. Starting material listed in pharmacopeias
4. Starting materials not listed in pharmacopeias

4.1. Starting materials of non-biological origin
4.2. Starting materials of biological origin

2.3.P.2.5 Minimizing the risk of TSE

2.3.P.2.6. Media preparation

2.3.P.2.7. In-process control tests

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

Critical Step	Controls (parameters/ limits/ frequency of testing).

2.3.P.2.8 Process validation

2.3. P.3 Control Tests on the finished IVP

2.3.P.3.1 Specifications

Brief information on finished product tests performed on each batch, including the batch release specification.

2.3.P.3.2 Analytical Methods

Summary of the analytical procedures to test the finished product specifications.

2.3.P.3.3 Validation of Analytical Procedures

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

2.3. P.4 Batch to Batch Consistency

a. Description of the lots:

Strength and batch number	Batch size	Date and site of production	Use

b. Summary of Results from the three consecutive batches in tabular form for ease of comparison.

2.3. P.5 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.)

b. Summary of the container and closure system.

2.3. P.6 Stability of the Finished Immunogenic Product

2.3.P.6.1 Protocols and results of the stability study

Protocol and results that justify the proposed validity period. Summary of stability data.

2.3.P.6.2 In- use shelf life

Stability-indicating tests should be provided on at least 2 different batches to support an in-use shelf life.

2.3.P.6.3 Description of procedures to guarantee cold chain

2.3. D INFORMATION ON DILUENT

For any immunological veterinary product accompanied with reconstitution diluents provide a summary of data to support the quality of reconstitution diluents.

Appendix 7. DETAILS ON THE MANUFACTURING PROCESS

1. Production and Quality control of Synthetic Peptides

The detail of the peptide synthesis including purification procedures shall be provided.

2. Conjugates and Modified Immunogenic Substances

This section of the guidance refers to immunogenic substances derived from another immunogenic substance or intermediate through chemical or enzymatic modification.
E.g. conjugation of an immunogen to a carrier molecule, enzymatic or chemical cleavage, and purification of the non-toxic subunit of a toxin, or derivatization. The modification may change the fundamental immunogenicity, toxicity, stability, or pharmacokinetics of the source immunogenic substance. The derived immunogenic substance may include linking moieties and new antigenic epitopes.

2.1. Manufacturing procedure

This section should provide a detailed description of:
The specifications and acceptance criteria, for the native immunogenic substance starting materials, which assure suitability for conjugation or modification.
The conditions of all reactions and/or syntheses used to produce a semi-synthetic conjugated molecule, derivatized molecule, or subunit, including intermediate forms of the reactants and immunogenic substance; also include the process parameters which are monitored, in-process controls, testing for identity and biologic activity, and any post-purification steps performed to produce a stabilized derived immunogenic substance.
The application should include a description of the methods and equipment used for the separation of unreacted materials and reagents from the conjugate, derivative, or subunit, and a rationale for the choice of methods.

2.2.Specification

Specifications should be provided for each modified immunogenic substance, including identity, purity, potency, physical-chemical measurements, and measures of stability. If test results for the derived substance will be reported for final release of the immunogenic product a validation report, to include estimates of variability and upper and lower limits, should be provided for each specification. Specifications should include the amount of unreacted starting materials and process reagents unless their removal has been validated.

2.3.Guidance for genetic constructs and recombinant cell lines

For recombinant DNA (rDNA) derived products and rDNA-modified cell substrates, detailed information shall be provided regarding the host cells and the source and function of the component parts of the recombinant gene construct.

2.4. Host cells

A description of the source, relevant phenotype, and genotype shall be provided for the host cell used to construct the biological production system. The results of the characterization of the host cell for phenotypic and genotypic markers including those that will be monitored for cell stability, purity, and selection shall be included.

2.5.Gene construct

A detailed description of the gene, which was introduced into, the host cells, including both the cell type and origin of the source material shall be provided. A description of the method(s) used to prepare the gene construct and a restriction enzyme digestion map of the construct shall be included.
The complete nucleotide sequence of the coding region and regulatory elements of the expression construct, with translated amino acid sequence, shall be provided including annotation designating all important sequence features.

2.6.Vector

Detailed information regarding the vector and genetic elements shall be provided, including description of the source and function of the component parts of the vector e.g. origins of replication, antibiotic resistance genes, promoters, and enhancers. A restriction enzyme digestion map indicating at least those sites used in construction of the vector shall be provided. Critical genetic markers for the characterization of the production cells shall also be indicated.

2.7.Final gene construct

A detailed description shall be provided of the cloning process, which resulted in the final recombinant gene construct. The information shall include a step-by-step description of the assembly of the gene fragments and vector or other genetic elements to form the final gene construct. A restriction enzyme digestion map indicating at least those sites used in constructions of the final product construct shall be provided.

2.8.Cloning and establishment of the recombinant cell lines

Depending on the methods to be utilized to transfer a final gene construct or isolated gene fragments into its host, the mechanism of transfer, copy number, and the physical state of the final construct inside the host cell (i.e. integrated or extra chromosomal) shall be provided. In addition, the amplification of the gene construct, if applicable, selection of the recombinant cell clone and establishment of the seed shall be completely described.

3. Cell banks

A description of the cell bank procedures used shall be provided including:

a) The cell bank system used
b) The size of the cell banks
c) The container and closure system used
d) A detailed description of the methods, reagents and media used for preparation of the cell banks
e) The conditions employed for cryopreservation and storage
f) In-process control(s) and Storage conditions
g) A description shall be provided for the procedures used to avoid microbial contamination and cross-contamination by other cell types present in the facility, and the procedures that allow the banked cells to be traced.

3.1. Master Cell Bank (MCB)

A complete history and characterization of the Master Cell Bank (MCB) shall be provided, including, as appropriate for the given cells:

a) The biological or chemical method used to derive the cell bank
b) Biochemistry (cell surface markers, isoenzyme analysis, specific protein or mRNA, etc.), Specific identifying characteristics (morphology, serotype etc.)
c) Karyology and tumorigenicity
d) Virulence markers

e) Genetic markers
f) Purity of culture
g) Media and components (e.g. serum)

3.2. Working Cell Bank (WCB)

This section shall also contain a description of the procedures used to derive a WCB from the MCB. The description should include the identification system used for the WCB as well as the procedures for storage and cataloguing of the WCB. The assays used for qualification and characterization of each new WCB shall be included with the results of those assays for the WCB currently in use. If applicable, a description of animal passage of the WCB performed to assure the presence of virulence factors, which are protective antigens, shall be supplied.

3.3. Production Cells

For r-DNA derived immunogenic substances, a detailed description of the characterization of the Production cells that demonstrates that the biological production system is consistent during growth shall be provided. The results of the analysis of the Production cells for phenotypic or genotypic markers to confirm identity and purity shall be included. This section should also contain the results of testing supporting the freedom of the Production cells from contamination by adventitious agents. The results of restriction enzyme analysis of the gene constructs in the cells 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.

3.4. Cell Growth and Harvesting

This section shall contain a description of each of the following manufacturing processes, as appropriate. The description should contain sufficient detail to support the consistency of the manufacture of the immunogenic substance.

3.5. Propagation

This section shall contain a description of:

a) Each step in propagation from retrieval of the WCB to culture harvest (stages of growth)

b) The media used at each step (including water quality) with details of their preparation and sterilization

c) The inoculation and growth of initial and sub-cultures, including volumes, time and temperatures of incubation(s)
d) How transfers are performed
e) Precautions taken to control contamination
f) In-process testing which determines inoculation of the main culture system
g) In-process testing to ensure freedom from adventitious agents, including tests on culture cells, if applicable.
h) The nature of the main culture system including operating conditions and control parameters (e.g. temperature of incubation, static vs. agitated, aerobic vs. anaerobic, culture vessels vs. fermenter, volume of fermenter or number and volume of culture vessels)
i) The parallel control cell cultures, if applicable, including number and volume of culture vessels
j) Induction of antigen, if applicable
k) The use of antibiotics in the medium and rationale, if applicable

3.6. Harvest

A description of the method(s) used for the separation of crude substances from the propagation system (precipitation, centrifugation, filtration, etc.) shall be provided. A brief description shall be given for the following:

a) The process parameters monitored
b) The criteria for harvesting
c) The determination of yields and
d) The criteria for pooling more than one harvest, if applicable
e) A description of the procedures used to monitor bioburden (including acceptance limits) or sterility shall be included. If the harvested crude immunogenic substance is held prior to further processing, a description of storage conditions and time limits shall be provided.

Appendix 8. DETAILS ON THE CONTROL OF STARTING MATERIALS OF BIOLOGICAL ORIGIN

1. Cell seed materials

General Requirements

If a virus can be grown efficaciously on cell cultures based on a seed lot system of established cell lines, no mammalian primary cells should be used. Permanently infected cells shall comply with the appropriate requirements described below. The cells must be shown to be infected only with the agent stated.

1.1. Requirements for Cell Lines

Cell seed materials used in manufacture shall normally be produced according to a Seed Lot System. Each Master Cell Seed (MCS) shall be assigned a specific code for identification purposes. The MCS shall be stored in aliquots at -70 °C or lower. Production of vaccine shall not normally be undertaken on cells further than 20 passages from the MCS.
Where suspension cultures are used, an increase in cell numbers equivalent to approximately three population doublings should be considered equivalent to one passage.
If cells beyond this passage level are to be used for production, the applicant should demonstrate, by validation or further testing, that the production cells are essentially similar to the MCS with regard to their biological characteristics and purity and that use of such cells has no deleterious effect on vaccine production.

The history of the cell line must be known in detail and recorded in writing (e.g. origin, number of passages, and media used for their multiplication, storage conditions).

The manufacturer must describe the method of preserving and using the cells, including details of how it is ensured that the maximum number of passages permitted is not exceeded during product manufacture. A sufficient number of MCS and Working Cell Seed (WCS) must be kept available for testing by the licensing authorities.
The checks described below should be carried out on a culture of the MCS and WCS or on cells from the WCS at the highest passage level used for production (see Table 1) and derived from a homogeneous representative sample. The representative nature of this sample must be proven.

Table 1: Stages of cell culture at which testing shall be carried out

	MCS	WCS	Cells from WCS at highest passage level

General microscopy	+	+	+
Bacteria/fungi	+	+	-
Mycoplasma	+	+	-
Viruses	+	+	-
Identification of species	+	-	+
Karyology	+	-	+
Tumourigenicity	+	-	-

1.1.1. Extraneous contaminants

General

The cells must be checked for their appearance under the microscope, for their rate of growth and for other factors which will provide information on the state of health of the cells.

a. Bacteria and fungi

The cells must be checked for contamination with bacteria or fungi. Contaminated cells must be discarded.

b. Mycoplasma

The cells must be checked for freedom from mycoplasma and pass the test for freedom from mycoplasma.

c. Viruses

The cells must not be contaminated by viruses and the checks must be performed in the following manner:

The monolayers tested must be at least 70 cm2, prepared and maintained using medium and additives, and grown under similar conditions to those used for the preparation of the biological product. The monolayers must be maintained in culture for a total of at least 28 days. Subcultures should be made at 7-days intervals unless the cells do not survive for this length of time when the subcultures should be made on the latest day possible. Sufficient cells, in suitable containers, must be produced for the final subculture to carry out the tests specified below. The monolayers must be examined regularly throughout the incubation period for the possible presence of cytopathic effects (cpe) and at the end of the observation period for cpe, haemadsorbent viruses, and specific viruses by immunofluorescence and other appropriate tests as indicated below.

- Detection of cytopathic viruses

  Two monolayers of at least 6 cm2 each must be stained with an appropriate cytological stain.

Examine the entire area of each stained monolayer for any inclusion bodies, abnormal numbers of giant cells or any other lesion indicative of a cellular abnormality which might be attributable to a contaminant.

- Detection of haemadsorbent viruses

  Monolayers totaling at least 70 cm2 must be washed several times with an appropriate buffer and a sufficient volume of a suspension of appropriate red blood cells added to cover the surface of the monolayer evenly. After different incubation times examine cells for the presence of haemadsorption.

- Detection of specified viruses

  Tests should be carried out for freedom of contaminants specific for the species or origin of the cell line and for the species for which the product is intended. Sufficient cells on appropriate supports must be prepared to carry out tests for the agents specified. Appropriate positive controls must be included in each test. The cells are subjected to appropriate tests using fluorescein-conjugated antibodies or similar reagents.

- Tests in other cell cultures

  Monolayers totaling at least 140 cm2 are required. The cells must be frozen and thawed at least 3 times and then centrifuged to remove cellular debris. Inoculate aliquots onto the following cells at any time up to 70% confluency:
  - Primary cells of the source species
  - Cells sensitive to viruses pathogenic for the species for which the vaccine is intended
  - Cells sensitive to pestiviruses

  The inoculated cells must be maintained in culture for at least 7 days, after which freeze-thawed extracts should be prepared as above, and inoculated onto sufficient fresh cultures of the same cell types to allow for the testing as described below. The cells are incubated for at least a further 7 days. All cultures must be regularly examined for the presence of any cytopathic changes indicative of living organisms. At the end of this period of 14 days, the inoculated cells must be subjected to the following checks:
  - Freedom from cytopathic and haemadsorbent organisms must be tested for, using the methods specified above.
  - Relevant substrates are tested for the absence of pestiviruses and other specific contaminants by immunofluorescence as indicated above.

1.1.2. Identification of species

It must be shown that the MCS and the cells from the WCS at the highest passage level used for production come from the species of origin specified by the manufacturer. This must be demonstrated by one validated method. When a fluorescence test is carried out and the corresponding serum to the species of origin of cells is used and shows that all the tested cells are fluorescent, it is not necessary to carry out other tests with reagents able to detect contamination by cells of other species.

1.1.3. Karyology

The cell lines used must be examined in the following manner:
A minimum of 50 cells undergoing mitosis must be examined in the MCS and a passage level at least that of the highest to be used in production. Any chromosomal marker present in the MCS must also be found in the high passage cells. The modal number of chromosomes in these cells must not be more than 15% higher than that of the MCS. The karyotypes must be identical. If the modal number exceeds the level stated, the chromosomal markers are not found in the WCS cells or the karyotype differs, the cell line may not be used for the manufacture of biological products.

1.1.4. Tumourigenicity

The potential risk of a cell line for the target species should be evaluated and, if necessary, tests should be carried out.

1.2. Requirements for primary cells

For most of mammalian vaccines, the use of primary cells is not acceptable for the manufacture of vaccines. If a vaccine has to be produced on primary cells, they should be obtained from a specific pathogen free herd or flock with complete protection from the introduction of diseases (e.g. disease barriers, filters on air inlets, no new animals introduced without appropriate quarantine). In the case of chicken flocks, these should comply with the requirements of the European Pharmacopoeia monograph for SPF chickens. For all other animals and species of birds, the herd or flock must be shown to be free from appropriate pathogens. All the breeding stock in the herd of flock intended to be used to produce primary cells for vaccine manufacture must be subject to a suitable regime such as regular serological checks carried out at least twice a year and two supplementary serological examinations performed in 15% of the breeding stock in the herd between the two checks mentioned above.

Wherever possible, particularly for mammalian cells, a seed lot system should be used with, for example, MCS formed from less than 5 passages, the WCS being no more than 5 passages from the initial preparation of the cell suspension from the animal tissues. Each MCS, WCS and cells

of the highest passage of primary cells must be checked in accordance with Table 2 and the procedure described below. The sample tested will cover all the sources of cells used for the manufacture of the batch. No batches of vaccine manufactured using the cells may be marketed if any one of the checks performed produces unsatisfactory results.

Table 2: Stages of primary cell culture at which testing shall be carried out

	MCS	**WCS**	**Cells from WCS at highest passage level**
General microscopy	+	+	+
Bacteria/fungi	+	+	–
Mycoplasma	+	+	–
Viruses	+	+	–
Identification of species	+	–	–

Extraneous contaminants

See sections under 1.1.1. above.

1.2.1. Tests in other cell cultures

Monolayers totaling at least 140 cm^2 are required. The cells must be frozen and thawed at least 3 times and then centrifuged to remove cellular debris. Inoculate aliquots onto the following cells at any time up to 70% confluency:

- Cells sensitive to viruses pathogenic for the species for which the vaccine is intended;
- Cells sensitive to pestiviruses.

The inoculated cells must be maintained in culture for at least 7 days, after which freeze-thawed extracts should be prepared as above, and inoculated onto sufficient fresh cultures of the same cell types to allow for the testing as described below. The cells are incubated for at least a further 7 days.

All cultures must be regularly examined for the presence of any cytopathic changes indicative of living organisms. At the end of this period of 14 days, the inoculated cells must be subjected to the following checks:

- Freedom from cytopathic and haemadsorbent organisms must be tested for using the methods specified in above.

- Relevant substrates are tested for the absence of pestiviruses and other specific contaminants by immunofluorescence as indicated above.

1.2.2. Identification of species

It must be shown that the MCS comes from the species or origin specified by the manufacturer (see Table 2). This must be demonstrated by one validated method. When a fluorescence test is carried out and the corresponding serum to the species or origin of cells is used and shows that all the tested cells are fluorescent, it is not necessary to carry out other tests with reagents able to detect contamination by cells of other species.

1.2.3. Requirements for embryonated eggs

Embryonated eggs must be obtained from a specific pathogen free (SPF) flock.

1.2.4. Requirements for animals

Animals must be free from specific pathogens, as appropriate to the source species and the target animal.

2. Seed Materials

2.1. Master seeds

2.1.1. Virus seed

General requirements

Viruses used in manufacture shall be derived from a Seed Lot System. Each Master Seed Virus (MSV) shall be tested as described below.
A record of the origin, passage history (including purification and characterisation procedures) and storage conditions shall be maintained for each Seed Lot. Each MSV shall be assigned a specific code for identification purposes. The MSV shall normally be stored in Aliquots at -70°C or lower if it is in liquid form or at -20°C or lower if in a lyophilized form. Production of vaccine shall not normally be undertaken using virus more than 5 passages from the MSV.

In the tests described in sections below, the organisms used shall not normally be more than 5 passages from the MSV at the start of the tests unless otherwise indicated.

Where the MSV is contained within a permanently infected MCS, the following tests shall be carried out on an appropriate volume of virus from disrupted MCS.

Where relevant tests have been carried out on disrupted cells to validate the suitability of the MCS, these tests need not be repeated.

a. Propagation

The MSV and all subsequent passages shall be propagated on cells, on embryonated eggs or in animals which have been shown to be suitable for vaccine production. All such propagations shall only involve substances of animal origin that meet the requirements of the Guideline on requirements for the production and control of immunological veterinary medicinal products (EMA/CVMP/IWP/206555/2010 Rev.1) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/12/WC500218307.pdf

b. Identity

The MSV shall be shown to contain only the virus stated. A suitable method shall be provided to identify the vaccine strain and to distinguish it as far as possible from related strains.

c. Sterility and mycoplasma

The MSV shall pass the tests for sterility and freedom from mycoplasma.

d. Extraneous agents

Serum containing a high level of neutralizing antibody to the virus of the Seed Lot shall be prepared, using antigen that is not derived from any passage level of the virus isolate giving rise to the MSV. Where it is not possible to prepare such a serum, other methods may be used to remove selectively the virus of a seed lot.

Sera shall be prepared on a batch basis. Each batch shall be shown to be free of antibodies to potential contaminants of the seed virus. Each batch shall be shown to be free of any non-specific inhibition effects on the ability of viruses to infect and propagate within cells (or eggs – if applicable). Each batch shall be treated at 56 °C for 30 minutes to inactivate complement.

Using a minimum amount of serum prepared as above, a sample of the MSV shall be treated so that all the vaccine is neutralized or removed. The final virus/serum mixture shall contain at least the virus content of 10 dose of vaccine per ml if possible. The mixture should then be tested for freedom from extraneous agents as follows.

The mixture shall be inoculated onto cultures of at least 70 cm2 of the required cell types. The cultures may be inoculated at any stage of growth up to 70% confluency. At least one monolayer

of each type must be retained as a control. The cultures must be monitored daily for a week. At the end of this period the cultures are freeze-thawed 3 times, centrifuged to remove cell debris and re-inoculated onto the same cell type as above. This is repeated twice. The final passage must produce sufficient cells in appropriate vessels to carry out the tests below.

Cytopathic and haemadsorbing agents are tested for using the methods above. Techniques such as immunofluorescence should be used for the detection of specific contaminants as described above. The MSV is inoculated onto:

- Primary cells of the species of origin of the virus;
- Cells sensitive to viruses pathogenic for the species for which the vaccine is intended;
- Cells sensitive to pestiviruses.

If the MSV is shown to contain living organisms of any kind, other than virus of the species and strain stated, then it is unsuitable for vaccine production.

2.1.2. Bacterial seed

General requirements

The bacteria used in the vaccine shall be stated by genus and species (and varieties where appropriate).
The origin, date of isolation, and designation of the bacterial strains used shall be given, and details provided, where possible, of the passage history, including details of the media used at each stage. Bacteria used in manufacture shall be derived from a Seed Lot System wherever possible. Each Master Seed Lot, (henceforth known as Seed Lot) shall be tested as described below.
A record of the origin, passage history (including purification and characterization procedures) and storage conditions shall be maintained for each Seed Lot. Each Seed Lot shall be assigned a specific code for identification purposes.

a. Identity and purity

Each Seed Lot shall be shown to contain only the species and strain of bacterium stated. A brief description of the method of identifying each strain by biochemical, serological and morphological characteristics and distinguishing it as far as possible from related strains shall be provided, as shall also the methods of determining the purity of the strain. If the Seed Lot is shown to contain living organisms of any kind other than the species and strain stated, then it is unsuitable for vaccine production.

b. Seed lot requirements

The minimum and maximum number of subcultures of each Seed Lot prior to the production stage shall be specified. The methods used for the preparation of seed cultures, preparation of suspensions for seeding, techniques for inoculation of seeds, titre and concentration of inocula and the media used shall be described. It shall be demonstrated that the characteristics of the seed material (e.g. dissociation or antigenicity) are not changed by these subcultures.
The conditions under which each seed lot is stored shall be described.

2.2. Working seed

Working seed shall be derived from one or more container of the Master seed. Working Seed shall be characterized in the same way as working cell bank (WCB).

2.3. Other substances of animal origin

All other substances, used in vaccine production shall be prepared in such a way as to prevent contamination of the vaccine with any living organism or toxin.