

**TANZANIA FOOD AND DRUGS AUTHORITY**



**GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION  
OF IMMUNOLOGICAL VETERINARY PRODUCTS**

**First Edition**

**June 2017**

P. O. Box 77150, EPI Mabibo, Off Mandela Road, Dar es Salaam, Tanzania  
Tel: +255-22-2450512/2450751/2452108, Fax: +255-22-2450793  
Website: [www.tfda.go.tz](http://www.tfda.go.tz), Email: [info@tfda.go.tz](mailto:info@tfda.go.tz)

## TABLE OF CONTENTS

ABBREVIATIONS.....	iv
ACKNOWLEDGEMENTS.....	vi
FOREWORD.....	vii
INTRODUCTION.....	1
GLOSSARY OF TERMS.....	2
MODULE 1: ADMINISTRATIVE INFORMATION.....	4
1.1 Comprehensive Table of Contents for all Modules.....	4
1.2 Motivation Letter.....	4
1.3 Manufacturing and Marketing Authorization.....	4
1.4 Application Information.....	4
1.4.1 Language.....	4
1.4.2 Application form.....	4
1.5 Product Information and Labelling.....	4
1.5.1 Summary of Product Characteristics (SmPC).....	4
1.5.2 Product Labelling.....	5
1.5.3 Information Leaflet.....	5
1.5.4 Samples.....	5
1.5.5 Samples of Finished Product.....	5
1.6 List of Countries where the Product has been Licensed.....	5
1.7 Good Manufacturing Practice (GMP).....	5
MODULE 2: OVERVIEWS AND SUMMARIES.....	6
2.1 Table of contents of Module 2.....	6
2.2 CTD Introduction.....	6
2.3 Overall Quality Summary (QOS).....	6
2.3. S Immunogenic Veterinary Substance .....	6
2.3. S.1 General Information (name, manufacturer).....	6
2.3. S.2 Manufacture (name, physical address).....	6
2.3. S. 3 Precautions against contamination.....	6
2.3. S.4 Control of immunogenic Substance.....	6
2.3. S.5 Container Closure System.....	7
2.3. S.6 Stability.....	7
2.3. P Immunogenic Veterinary Product.....	7
2.3. P.1 Qualitative and Quantitative Composition.....	7
2.3. P.2 Manufacture (name, physical address).....	7
2.3. P. 3 Precautions against contamination.....	7
2.3. P.4 Control Tests on the Finished Product.....	7
2.3. P.5 Container Closure System.....	7
2.3. P.6 Stability.....	7
MODULE 3: QUALITY INFORMATION.....	8
3.1 Table of Contents of Quality Part.....	8
3.2.S Immunogenic substance(s).....	8
3.2.S.1 General information,.....	8

3.2.S.2 Manufacturing Process for Immunogenic Substance(S).....	8
3.2.S.6 Bulk antigen Container and Closure System.....	14
3.2.S.7 Stability of immunogenic substance.....	15
3.2.P IMMUNOLOGICAL VETERINARY PRODUCT (IVP).....	15
3.2. P.1 Description and Composition of the IVP.....	15
3.2. P.1.1 Description of the dosage form.....	15
3.2. P.1.2 Qualitative and Quantitative Particulars.....	15
3.2.P.2 Method of manufacture.....	16
3.2.P.3 Manufacturing process.....	16
3.2.P.4 Control of Starting Materials.....	16
3.2.P.5 Minimising the risk of TSE.....	20
3.2.P.6 Media preparation.....	20
3.2.P.7 In-process control tests.....	20
3.2. P. 8 Process Validation.....	20
3.2.P.9 Control Tests on the Finished Product.....	21
3.2.P.10 Description of batch identification system.....	22
3.2.P.11 Batch to batch consistency.....	22
3.2.P.12 Containers.....	22
3.2.P. 13 Stability of the Final Product.....	22
3.2.P.13.2 In-use shelf life.....	23
3.3. D Manufacturing and controls of Reconstitution diluents.....	24
3.3. D.1 Qualitative and Quantitative Particulars.....	25
MODULE 4: SAFETY.....	26
4.1 Table of contents of Module 4.....	26
4.2 Report on studies.....	26
4.2.1 Laboratory Tests.....	26
4.2.1.1 Single dose toxicity studies.....	26
4.2.1.2 Overdose toxicity studies.....	26
4.2.1.3 Repeated dose toxicity studies.....	26
4.2.1.4 Other Safety studies (for live attenuated vaccines).....	27
4.2.2. Field Safety.....	27
4.2.3 Other Safety issues to be considered.....	27
4.2.3.1 Safety to the user.....	27
4.2.3.2 Safety to the environment.....	27
4.2.3.3 Safety of residues.....	27
4.2.3.4 Interactions:.....	28
MODULE 5: EFFICACY.....	29
5.1 Table of contents for Module.....	29
5.2 Efficacy studies Reports.....	29
5.2.1 Laboratory Efficacy.....	29

5.2.2 Field Efficacy.....	30
APPENDIX I: APPLICATION FORM .....	31
ANNEX II: SUMMARY OF PRODUCT CHARACTERISTICS.....	37
ANNEX III: CONTAINER LABELLING.....	43
ANNEX IV: INFORMATION LEAFLET.....	43
ANNEX V: QUALITY OVERALL SUMMARY-(QOS).....	49

## **ABBREVIATIONS**

**AEFI:** Adverse Event Following Immunization

**ATCvet:** The Anatomical Therapeutic Chemical code.

**BP:** British Pharmacopoeia

**EMA:** European Medicines Agency.

**EMEA:** European Medicines Evaluation Agency ( Now known as EMA).

**GMO:** Genetically modified organism

**Hrs:** Hours

**IFAH:** International Federation of Animal Health

**INN:** International Non-proprietary Name

**IVP:** Immunological Veterinary Product

**IWP:** Immunological Working Party, a subgroup of the CVMP in the EU

**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

**TSE:** Transmissible Spongiform Encephalopathy

**WCB:** Working Cell Bank

**WCS:** Working Cell Seed

**VICH:** The International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products.

**VICH GL:** VICH Guideline

**WSV:** Working Cell Virus

**CFR:** Code of Federal Regulations, Title 9, Animals and Animal Products

**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

**SPF:** Specific Pathogen Free

**WHO:** World Health Organisation

**USP:** United States Pharmacopoeia

## **ACKNOWLEDGEMENTS**

This is the first edition of the Guidelines on Submission of Documentation for Registration of Immunological Veterinary Products to be introduced by TFDA. This is more specific guideline for documentation for registration of veterinary biological product.

In reviewing the current guidelines, several TFDA staff and experts were involved in the process to include the following:

- a. Mr. Akida M.Khea
- b. Mr. Sunday Kisoma
- c. Dr. Emmanuel E. Mutakyahwa
- d. Ms. Rosemary Aaron
- e. Ms. Anita Bitegeko
- f. Christopher Migoha
- g. Dr. Rukia Saidi
- h. Dr. Athanas Mseki

I am truly indebted for their tireless efforts in collecting and amassing the information for readers to construe what has been delineated in this document.

Several international guidelines to include The International Conference on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products guidelines and World Organisation for Animal Health guidelines were referred during review. I once again thank all those who made these guidelines easily available for adoption and/or adaption.

Members of the Veterinary Medicines Registration Technical Committee are also acknowledged for their scientific and well-thought inputs when discussing the revised guidelines.



**Adam Mitangu Fimbo**  
**Director, Medicines and Complementary Products**  
**Tanzania Food and Drugs Authority**

## **FOREWORD**

Tanzania Food and Drugs Authority (TFDA) was established under the Tanzania Food, Drugs and Cosmetics Act Cap 219, 2003 with the mission of protecting and promoting public health by ensuring quality, safety and effectiveness of food, medicines (including veterinary medicines), cosmetics and medical devices. The first step towards achieving this goal is to conduct pre-market control including evaluation of products so as to ensure that they meet standards of quality, safety and effectiveness before the products are allowed into the market. This is a fundamental requirement for authorisation of medicinal products including veterinary medicines in Tanzania.

In order to have consistent and uniform submissions, TFDA develops and issue application guidelines to provide guidance to applicants on content and format of minimum information required for registration of products. The current guidelines for registration of biological products have been in existence since June 2004.

Thus presentation of evidence on quality, safety and efficacy of veterinary biological products to national medicines regulatory authorities for obtaining registration must be updated to match with the new demands as per current broadened knowledge from the development veterinary biological researches. Such evidence is gathered during drug and formulation development and compiled into immunogenic products.


The present guidelines have therefore been reviewed in order to cope with the new developments in line with the requirements for marketing authorisation. The reviewed guidelines entitled “The Guidelines on Submission of Documentation for Registration of Veterinary Biological Products, 2017 provide guidance on the content and format of information to be presented in registration dossiers submitted to TFDA for registration of veterinary immunogenic products in Tanzania.

All applicants are encouraged to familiarize with the guidelines and follow them strictly when preparing and submitting applications for marketing authorization of veterinary immunogenic products. However, the guidelines are not intended to inhibit innovation and they only provide for minimum requirements thereby giving room for applicants to submit additional data.

Adherence to guidelines will ensure that all relevant information is submitted to facilitate efficient and effective evaluation as well as approval process. It will also help to avoid queries which often results in unnecessary delays in giving approvals



to new medicines thereby improving access to medicines of proven quality, safety and efficacy in the shortest possible time.



**Hiiti B. Sillo**  
**Director General**  
**Tanzania Food and Drugs Authority**

## **INTRODUCTION**

Section 51 (1) of the Tanzania Food, Drugs and Cosmetics Act, 2003 provides conditions for registration of medicines in Tanzania. These conditions include:

- (a) The availability of the medicine is in the public interest;
- (b) The medicine is safe, efficacious and of acceptable quality;
- (c) The premises and manufacturing operations comply with the current Good Manufacturing Practices requirements as provided in the regulations;
- (d) The medicine complies with any other requirements as may be prescribed by the Authority.

Furthermore, Section 22 (1) of the Act prohibits the sell, supply or importation of any drug unless it is registered under the provisions of the Act.

These guidelines prescribe data required to demonstrate that a Veterinary Immunological Product which is the subject of registration conforms to the requirements of the Act and regulation above.

The “Guidelines sets out procedures and requirements for the implementation of Medicinal Products Registration through Common Technical Document (CTD). The CTD has five Modules:

Module 1: Administrative Requirements;

Module 2: Overviews and Summaries of Veterinary,

Module 3: Quality of the Veterinary immunogenic substance(s) and Veterinary immunological products (IVP),

Module 4: Safety

Module 5: Efficacy

These guidelines apply only to veterinary immunological products. In the case of other medicinal products such as human medicinal products, veterinary medicinal products and herbal drugs, separate guidelines are available and these can be accessed online from TFDA website; [www.tfda.go.tz](http://www.tfda.go.tz).

Applicants are also requested to read these guidelines together with the Tanzania Food, Drugs and Cosmetics Act, 2003 and Regulations made there under.

## **GLOSSARY OF TERMS**

### **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 recognised by the host it may be linked to a carrier for the purposes of inducing antibodies. Such small antigens are known as haptens.

### **Applicant**

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

### **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 a number of sub batches, which are further processed in one process or a series of processes, so that each sub batch can be expected to be homogenous.

### **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)**

A collection of aliquots of a 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 a 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.

**Working Cell Seed (WCS)**

A collection of aliquots of a 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 to 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.

**Vaccine**

A preparation of a weakened (attenuated) or killed pathogen, 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.

## **MODULE 1: ADMINISTRATIVE INFORMATION**

Module 1 should contain all administrative documents (for example, application forms and certifications), labeling, general correspondence and annexes (drug residue assessments and antibiotic resistance evaluation reports), as needed. Documents should be organized in the order listed below. Generally, all the documents in Module 1, other than the annexes, can be provided in a single volume.

Products should be evaluated on a First in First out (FIFO) basis and the timeline for review and communication to applicant should be within 240 days for imported Veterinary Medicines and 120 days for domestically manufactured Veterinary Medicines.

### **1.1 Comprehensive Table of Contents for all Modules**

Table of contents should indicate the sections, subsection and corresponding page numbers for the entire application.

### **1.2 Motivation Letter**

Motivation letter of not more than 500 words should be submitted with the product dossier indicating why the product should be registered in Tanzania. The letter should be signed by the Applicant.

### **1.3 Manufacturing and Marketing Authorization**

Certificate of Pharmaceutical Product (CPP) or an equivalent certificate issued by competent authority of the country of origin as per WHO format, should be submitted.

### **1.4 Application Information**

#### **1.4.1 Language**

All applications and supporting documents should be in Kiswahili or English.

### **1.4.2 Application form**

An application to register an Immunological product for veterinary use must be accompanied by a completed application form (**Annex I**)

The application form should be dully filled with relevant information and attachments, dated signed and stamped appropriately

### **1.5 Product Information and Labelling**

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

#### **1.5.1 Summary of Product Characteristics (SmPC)**

All applications for registration of Immunological Veterinary Products should be accompanied by SmPC. The Summary of Product Characteristics is not a promotional document. Statements of a promotional nature such as “x is the safest drug” should not be used in the SPC.

An applicant shall prepare and present prescribing information in the contents and format as provided in **annex II**.

#### **1.5.2 Product Labelling**

Product should be labelled as prescribed in **annex III** of this guideline.

#### **1.5.3 Information Leaflet**

Every container of a veterinary medicinal product should be accompanied with information leaflet.

Provide two copies of information on A4 paper and also specimens as they will appear with the commercial product.

The contents and format of the leaflet are as provided in **annex IV** of this guideline.

#### **1.5.4 Samples**

Samples, or alternatively labels and cartons, of the primary and secondary packaging of the product, including the package insert and accessories should be submitted.

#### **1.5.5 Samples of Finished Product**

Number of samples depends on the nature and type of the product applied for registration, ideally samples should be provided to allow full monograph analysis plus one repeated analysis.

## **1.6 List of Countries where the Product has been Licensed and Summary of Approval Conditions**

The list of countries where the product is registered at the time the application for registration should be submitted or, if there are none, the countries where registration is being processed should be listed. In the event the product has been registered in other countries, attach copies of registration certificates

## **1.7 Good Manufacturing Practice (GMP)**

For all medicines, irrespective of the country of origin, all key manufacturing and/or processing steps in the production of active pharmaceutical ingredient and finished veterinary medicinal products must be performed in plants that comply with TFDA GMP guidelines. Applicant should refer to TFDA Guidelines on Good Manufacturing Practice for more guidance.

## **MODULE 2: OVERVIEWS AND SUMMARIES**

### **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 Overall Quality Summary (QOS)**

The Quality Overall Summary (QOS) 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 in other parts of the CTD.

The QOS template is in **annex V** of this guideline. The QOS should be provided in both word and PDF version, the word version is a must. Complete the Quality Overall Summary (QOS) following the following guidance below:

### **2.3. S Immunogenic veterinary Substance (name, manufacturer)**

#### **2.3. S.1 General Information (name, manufacturer)**

Information from 3.2.S.1 should be included.

#### **2.3. S.2 Manufacture (name, physical address)**

Information from 3.2.S.2 should be included: i.e.

Information on the manufacturer as provided in 3.2. S.2.1

A simple flow diagram of showing of the manufacturing process as provided in 3.2.S.2.3

A brief description of the manufacturing process and the controls as provided in 3.2.S.2.2

#### **2.3. S. 3 Precautions against contamination**

Information concerning precautions taken to prevent contamination or cross contamination during preparation of cell banks and manufacturing, including areas for the handling of animals used in production should be provided.

#### **2.3. S.4 Control of immunogenic Substance**

A brief summary of the justification of the specification(s), the analytical procedures, validation and batch analysis of pivotal lot of immunogenic substance should be provided.

#### **2.3. S.5 Container Closure System**

A brief description and discussion of the information, from 3.2.S.6 should be included.

#### **2.3. S.6 Stability**

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life

### **2.3. P Immunogenic Veterinary Product (name, manufacturer)**

#### **2.3. P.1 Qualitative and Quantitative Composition**

Information from 3.2.P.1 should be included.

#### **2.3. P.2 Manufacture (name, physical address)**

Information from 3.2.P.2 should be included: i.e.

Information on the manufacturer as provided in 3.2. P.2.1



Simplified flow diagram showing the manufacturing process as provided in 3.2.P.2.2.1

Brief description of the manufacturing process and the controls as provided in 3.2.P.2.2.2

### **2.3. P. 3 Precautions against contamination**

Information concerning precautions taken to prevent contamination or cross contamination during preparation of cell banks and manufacturing.

### **2.3. P.4 Control Tests on the Finished Product**

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation should be provided. *Specification(s) from 3.2.P.9 should be provided.*

A tabulated summary of the batch analyses provided under 3.2.P.11, with graphical representation where appropriate should be included.

### **2.3. P.5 Container Closure System**

A brief description and discussion of the information, from 3.2.P.12 should be included.

### **2.3. P.6 Stability**

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions and shelf-life

## **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. 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 should be provided of physicochemical and other relevant properties of the immunogenic substance, including biological activity. The description of an 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 drug product.

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

### **3.2. S.2.1 Manufacturer(s)**

Declare the name(s) and physical address(es) of the manufacturer(s) of the immunogenic substance including activities performed at each manufacturing site.

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

### **3.2.S.2.2 Method of Manufacture**

#### **3.2. S.2.2.1 Flow chart of 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 Manufacturing Process**

Present a detailed description of each process step as presented in the flow chart or the immunogenic substance. 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 WSB as well as the procedures for storage and cataloguing 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. List all the components used in the manufacturing process including media, solvents or solutions should also be provided.

A description should be provided for:

#### **a) 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 yield, purity and viability (if applicable) of the crude harvest should also be included.

#### **b) 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. A description should be provided in assurance that:

- (i) Culture purity is verified before inactivation.
- (ii) The method(s) and agent(s) used for inactivation.
- (iii) The method(s) undertaken to prevent aggregation and assure homogeneous access of inactivating agent(s) to the culture.
- (iv) The stage in production where inactivation or killing is performed
- (v) The parameters which are monitored.

#### **c) Detoxification (if appropriate)**

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

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

#### **d) Purification (if appropriate)**

Describe any purification methods used, including specialised 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.

**e) Stabilisation process (if applicable)**

A description should be provided for any post-purification steps performed to produce a stabilised immunogenic substance (e.g. adsorption, addition of stabilisers, 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 shall also be given. 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.

**f) 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.

Consistency of the manufacturing process for each immunogenic substance component should be demonstrated by providing at least three lot certificates, preferably consecutive, batches of active immunogenic substance of a size corresponding to that for routine production.

**3.2. S.2.2.3. Manufacturing Consistency**

Consistency of the manufacturing process for each antigenic component should be demonstrated by providing the manufacturing of at least three, preferably consecutive, batches of 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.2.3 Production and Quality control of Synthetic Peptide**

The details of the peptide synthesis including purification procedures should be provided.

### **3.2.S.2.3.1 Manufacturing procedure**

This section should provide a detailed description of:

The specifications and acceptance criteria, for the 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, derivatised molecule, or subunit, including intermediate forms of the reactants and immunogenic substance should be stated. In addition, the process parameters which are monitored during in-process controls, testing for identity and biologic activity, and any post-purification steps performed to produce a stabilised derived immunogenic substance should be stated as well.

The application should include a description of the methods and equipment used for separation of unreacted materials and reagents from the conjugate, derivative, or subunit, and a rationale for the choice of methods.

### **3.2. S.2.3.2 Specification**

Specifications for each modified immunogenic substance, including identity, purity, potency, physical-chemical measurements, and measures of stability should be provided.

### **3.2. S.2.4 Guidance for genetic constructs and recombinant cell lines**

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

#### **3.2.S.2.4.1 Host cells**

A description of the source, relevant phenotype, and genotype for the host cell used to construct the biological production system should be provided.

#### **3.2.S.2.4.2 Gene construct**

A detailed description of the gene, which was introduced into, the host cells, including the cell type and origin of the source material should be provided. A description of the method(s) used to prepare the gene construct and a restriction enzyme digestion map of the construct should also be included.

The complete nucleotide sequence of the coding region and regulatory elements of the expression construct, with translated amino acid sequence should be provided including annotation designating all important sequence features.

#### **3.2. S.2.4.3 Vector**

Detailed information regarding the vector and genetic elements, 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 should be provided. A critical genetic markers for the characterization of the production cells should also be indicated.

#### **3.2. S.2.4.4 Final Gene Constructs**

Provide a detailed description of the cloning process which resulted in the final recombinant gene construct. The information should 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.

#### **3.2. S.2.4.5 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) should be provided. In addition, the amplification of the gene construct, if applicable, selection of the recombinant cell clone and establishment of the seed should be completely described.

#### **3.2.S.2.5 Cell banks**

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

- (a) The cell bank system used
- (b) The size of the cell banks
- (c) The container and closure system used
- (d) 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 used
- (g) 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.

##### **3.2.S.2.5.1 Master Cell Bank (MCB)**

A complete history and characterization of the Master Cell Bank (MCB) should be provided, including:

- (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 and
- (g) Media and components (e.g. serum)

##### **3.2.S.2.5.2 Working Cell Bank (WCB)**

Provide 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 should 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, should be supplied.

### **3.2.S.2.5.3 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 should be provided. Results of the analysis of production cells for phenotypic or genotypic markers to confirm identity and purity should be included. This section should also contain the results of testing to support the freedom of the production cells from contamination by adventitious agents. The results of restriction enzyme analysis of the gene constructs in the cells should also be submitted.

Detailed information on the characterization and testing of banked cell substrates should be submitted. This should include the results of testing to confirm the identity, purity and suitability of the cell substrates for manufacturing use.

### **3.2.S.2.5.4 Cell Growth and Harvesting**

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

### **3.2.S.2.5.5 Propagation**

Description should be provided on:

- (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 and
- (k) The use of antibiotics in the medium and rationale (if applicable).

#### **3.2.S.2.5.6 Harvest**

A description of the method(s) used for separation of crude substance from the propagation system (precipitation, centrifugation, filtration etc.) should be provided. Brief description should be given on:

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

#### **3.2.S. 2.5.7 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.6 Bulk antigen 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.7 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.7.1 Protocol of stability study, summary and conclusions**

Provide the stability protocol which including all the storage conditions (temperature, humidity, light) in which the immunogenic substance is evaluated

#### **3.2.S.7.2 Stability data**

Stability data should include complete data from each batch evaluated during stability studies.

#### **3.2.S.7.3 Storage and shipping conditions of immunogenic substance**

When applicable, describe the equipment used, areas, and buildings (if pertinent) and the shipping and storage conditions

### **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, 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 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, demineralised), 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 manufactures for production and quality control should be stated.

#### 3.2.P.2.2 Flow chart of 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.3 Manufacturing process

A detailed description of the manufacturing process of the IVP including the sterilisation 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.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.

### **3.2.P.4 1 Starting materials listed in pharmacopoeias**

### **3.2. P.4.2 Starting materials not listed in pharmacopoeias**

#### 3.2.P.4.2.1 Starting materials of non-biological origin

#### 3.2.P.4.2.2 Starting materials of biological origin

#### **3.2. P.4.2.2.1 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, provide supporting evidence that no mammalian primary cells is used in the culturing process.

#### **3.2. P.4.2.2.1.1 Preparation of Cell Lines**

Detailed description of preparation of Cell lines from the Cell seed materials described according to a Seed Lot System should be provided. The number of passages cell used in the vaccine production should be cleanly identified, in addition the storage condition of MCS should be given.

Where suspension cultures are used, an increase in cell numbers equivalent to approximately three population doublings should be considered equivalent to one passage.

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 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 should be given.

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 should be carried out**

	MCS	WCS	Cells from WCS at highest passage level
General microscopy	+	+	+
Bacteria/fungi	+	+	-
Mycoplasma	+	+	-

Viruses	+	+	-
Identification of species	+	-	+
Karyology	+	-	+
Tumourigenicity	+	-	-

### 3.2.P.4.2.1.2 Extraneous contaminants

An approved test protocol and test report for evincing the absence of cell contamination above the recommended limits from bacteria and fungi, mycoplasma and viruses should be provided

### 3.2.P.4.2.1.3 Requirements for primary cells.

For most of the 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 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 or 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 procedure and results should be provided

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

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

--	--	--	--

### **3.2.P.4.2.2 Seed Materials**

#### **3.2.P.4.2.2.1 Master seeds**

##### **i. Virus seed**

###### **(a) General requirements**

Viruses used in manufacture should be derived from a Seed Lot System. Each Master Seed Virus (MSV) should be tested as described and results provided.

###### **(b) Propagation**

The MSV and all subsequent passages should be propagated on cells, on embryonated eggs or in animals which have been shown to be suitable for vaccine production. All such propagations should only involve substance of animal origin that meet the requirements of section 1.1 of the [Adopted guidelines](#) “General requirements for the production and control of live mammalian bacterial and viral vaccines for veterinary use” (WC500004651) and “General requirements for the production and control of inactivated mammalian bacterial and viral vaccines for veterinary use”(WC500004652), effective date Sep 1992.

###### **(c) Identity**

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

###### **(d) Sterility and mycoplasma**

The MSV should pass the tests for sterility test against mycoplasma, bacterial and viral contamination test.

##### **ii. Bacterial seed**

###### **(a) General requirements**

The bacteria used in the vaccine should be stated by genus and species (and varieties where appropriate).

The origin, date of isolation and designation of the bacterial strains used should be given, and details provided, where possible, of the passage history, including details of the media used at each stage.

Bacteria used in manufacture should be derived from a Seed Lot System wherever possible. Each Master Seed Lot, (henceforth known as Seed Lot) should be tested and its evidence of its purity submitted

### **Seed lot requirements**

The minimum and maximum number of subcultures of each Seed Lot prior to the production stage should 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 should be provided.

#### **3.2.P.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 Module 1.

#### **3.2.P.6 Media preparation**

Details of methods of preparation and sterilisation 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.7 In-process control tests**

A description of all analytical testing performed to characterise 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 organised and fully indexed to enable easy access. Results for quantitative assays should be presented as actual data not generally as "Pass" or "Fail".

#### **Biological activity tests**

A description and results of all relevant in vivo and in vitro biological testing (bioassays) performed on the manufacturer's reference standard lot or other relevant lots to demonstrate the potency and activity (ies) of the immunogenic substance should be provided.

#### **3.2. P. 8 Process Validation**

A complete report, including protocols and results and control standard 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.

### **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.9 Control Tests on the Finished Product**

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 colour and clarity of the Immunological Veterinary Product.

#### **(b) Identity**

The method used to establish the identity of the IVP should be described. The description should include an evaluation of specificity and sensitivity of the method.

#### **(c) Purity/sterility**

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

#### **(d) Safety**

Provide results of the batch safety tests performed in the target animal species.

#### **(e) Potency/Titre**

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 inactivant, etc.

#### **(g) Sampling procedures (add information)**

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

**(h) Specifications and methods**

A description of all test methods selected to assure the identity, purity, titre /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. Certificates of analysis and analytical results for at least three consecutive batches should also be provided.

**(i) Validation results**

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.10 Description of batch identification system**

Define the lot in the stages of filling, lyophilization (if it applies) and packaging.

**3.2.P.11 Batch to batch consistency**

Provide at least three consecutive production batches of the IVP 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.

Provide the manufacturing records of these three batches.

**3.2.P.12 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 product, 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. 13 Stability of the Final 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.13.1 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 0 and end of shelf life
  - (b) Potency/virus titre/bacterial counts
  - (c) Physical and chemical tests, as appropriate, such as:
    - Moisture content of lyophilised 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 in 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.13.2 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.

#### **3.2.P.13.2.1 Shelf-life after first opening the container**

Generally, an in-use shelf life after 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.

### **3.2.P.13.2.2 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 titre 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.

### **3.2.P.13.2.3 Extended in-use shelf life:**

A CVMP guideline (EMEA/CVMP/IWP/250147/2008) on data requirements to support in-use stability claims for veterinary vaccines is available. <http://www.ema.europa.eu/pdfs/vet/iwp/25014708enfin.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 [http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general\\_content\\_000374.jsp&mid=WC0b01ac058002ddc5](http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000374.jsp&mid=WC0b01ac058002ddc5)

### **3.2. P.13.2.4 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.

### **3.3. D Manufacturing and controls of Reconstitution diluents**

For any IVP 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) Certificate of Good Manufacturing Practice
- (d) Valid Manufacturing Authorization for the production of the diluent(s)
- (e) Description of the reconstitution diluents(s)
- (f) Description of the container and closure system
- (g) Qualitative and Quantitative particulars
- (h) Specifications of container closure system along with certificates of analysis
- (i) Specification of reconstitution diluents(s) along with certificates of analysis
- (j) Description of manufacturing method production and control of starting materials
- (k) Control tests during the manufacturing process
- (l) Control tests of the finished product
- (m) Sterility tests

- (n) 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 labelling.
- (o) Process validation report
- (p) Analytical validation report
- (q) 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 official recognized document, signed by responsible personnel, dated with version control number.

### 3.3. D.1 Qualitative and Quantitative Particulars

A tabulated list of all components of the diluents (if applicable) should be given as per table 1 below. Name of diluents, Quantity per dosage unit and the reason(s) for inclusion of each excipient (if applicable) should be stated.

**Table 1: Composition of the Reconstitution Diluent(s)**

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

## **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.

##### **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 life time. 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.

#### **4.2.1.4 Other 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 absence of reversion to virulence."

d) Recombination or genomic re-assortment of strains

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

#### **4.2.2. 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 section 3.2.P.3.

### **4.2.3 Other Safety issues to be considered**

#### **4.2.3.1 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

#### **4.2.3.2 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.

#### **4.2.3.3 Safety of residues**

Residues studies are not normally required for immunological veterinary products, however the effects of residues of constituents of the vaccine such as adjuvants or live zoonotic organisms used as antigens should be considered if necessary. A suitable withdrawal period should be provided if necessary.

#### **4.2.3.4 Interactions:**

The safety of administering the immunological veterinary product at the same time or at the same site as another immunological veterinary medicinal product must be demonstrated if a recommendation for such use is to be made on the SPC.

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**

Tests in the target species of animal to demonstrate efficacy of the IVP to support the indications for which it will be used; details of the following studies should be provided. Reports on the range of studies done in target species are normally required

#### **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 3.2.P.3 of the dossier 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 potential decrease in efficacy when administered at the same time as other IVP (interference)

### **Each individual clinical 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 – end points
- (j) Details on – randomisation, blinding, compliance and justifications
- (k) Treatments given – identity and quality of the investigational and control products used, 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 section 3.2.P.3 of the dossier. 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.

TFDA/DMC/HVR/F/006

**APPENDIX I: APPLICATION FORM FOR REGISTRATION OF IMMUNOLOGICAL VETERINARY PRODUCT(S)**

Application Number	<b>For official use only</b>
Date of submission of the dossier	
Conclusion of the assessment <i>If the dossier is <b>RECOMMENDED</b> specify:</i> <ul style="list-style-type: none"> <li>• <i>Primary packaging and shelf-life of product,</i></li> <li>• <i>Storage condition of product and special precautions</i></li> <li>• <i>Distribution category</i></li> </ul>	<b>RECOMMENDED (no outstanding issues)</b> <b>QUERY RAISED/REJECTED</b>  <i>(Please delete which does not apply)</i>
<b>MODULE 1: ADMINISTRATIVE INFORMATION</b>	
1.0 PARTICULARS OF THE IMMUNOLOGICAL VETERINARY PRODUCT (IVP)	
1.1	Type of the medicinal product application

	New (Innovator) Generic Renewal
1.2	Proprietary Name
1.3	International Non-proprietary Name (INN) of the immunogenic substance
1.4	Strength of immunogenic substance(s) per unit dosage form:
1.5	Name and address (physical and postal) of Applicant
(Company) Name: Address: Country: Telephone: E-Mail:	
1.6	Dosage form and route of administration
1.6.1	Dosage form:
1.6.2	Route(s) of administration (
1.7	Packing/pack size:
1.8	Visual description (Add as many rows as necessary)
1.9	Proposed shelf life (in months):
1.9.1	Proposed shelf life (after reconstitution or dilution) (if applicable):
1.9.2	Proposed shelf life (after first opening container):
1.9.3	Proposed storage conditions:
1.9.4	Proposed storage conditions after first opening:
1.11	Pharmacotherapeutic group and ATC Code
1.11.1	Pharmacotherapeutic group:
1.11.2	ATC Code: (Please use current ATC code)

1.11.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made: <input type="checkbox"/>		
1.12	Distribution category: <input type="checkbox"/> POM (Prescription only Medicine) unless otherwise, provide justification)		
1.13	Country of origin:		
1.14	Product Marketing Authorization in the country of origin (Attach Certificate of Pharmaceutical Product from National Medicines Regulatory Authority). If not registered, state reasons		
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> <input type="checkbox"/> Authorised  Country:  Date of authorisation (dd-mm-yyyy):  Proprietary name:  Authorisation number:  <input type="checkbox"/> Refused  Country:  Date of refusal (dd-mm-yyyy):  Reason for Refusal: </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> <input type="checkbox"/> Withdrawn (by applicant after authorisation)  Country:  Date of withdrawal (dd-mm-yyyy):  Proprietary name:  Reason for withdrawal:  <input type="checkbox"/> Suspended/revoked (by competent authority)  Country:  date of suspension/revocation (dd-mm-yyyy):  Reason for suspension/revocation:  Proprietary name: </td> </tr> </table>		<input type="checkbox"/> Authorised Country: Date of authorisation (dd-mm-yyyy): Proprietary name: Authorisation number: <input type="checkbox"/> Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	<input type="checkbox"/> Withdrawn (by applicant after authorisation) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: <input type="checkbox"/> Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name:
<input type="checkbox"/> Authorised Country: Date of authorisation (dd-mm-yyyy): Proprietary name: Authorisation number: <input type="checkbox"/> Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	<input type="checkbox"/> Withdrawn (by applicant after authorisation) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: <input type="checkbox"/> Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name:		
1.15	List SRAs where the vaccine is approved.		
1.16	Name(s) and complete physical address(es) of the manufacturer(s)		
<b>1.16.1</b>	<p><b>Name(s) and physical address(es) of the manufacturing site of the Immunological veterinary product (IVP), including the final product release if different from the manufacturer. Alternative sites should be also declared here.</b></p> <p>All manufacturing sites involved in the manufacturing process of each step of the IVP, stating the role of each including quality control</p>		

	<p>/ in-process testing sites should be listed.</p> <p>(Add as many rows as necessary)</p>
<p>Name:</p> <p>Company name:</p> <p>Address:</p> <p>Country:</p> <p>Telephone:</p> <p>E-Mail:</p>	
<p><b>1.16.2</b></p>	<p><b>Name(s) and physical address(es) of the manufacturer(s) of the active immunogenic substance</b></p> <p>(Add as many rows as necessary)</p> <p>All manufacturing sites involved in the manufacturing process of each source of active immunogenic substance, including quality control / in-process testing sites should be listed.</p>
<p>Name:</p> <p>Company name:</p> <p>Address:</p> <p>Country:</p> <p>Telephone:</p> <p>E-Mail:</p>	
<p>1.17</p>	<p>Name and address (physical and postal) of the Local Technical Representative (if applicable)</p>
<p>Name:</p> <p>Company name:</p> <p>Address:</p> <p>Country:</p> <p>Telephone:</p> <p>E-Mail:</p>	

1.18	Name and address (physical and postal) of the person or company responsible for pharmacovigilance			
Name: Company name: Address: Country: Telephone: E-Mail:				
1.19	Qualitative and Quantitative composition of the immunogenic substance(s) and excipient(s)  A note should be given as to which quantity the composition refers (e.g. per ml).			
Name of immunogen(s)	Quantity / dosage unit	Unit of measure	Reference/ monograph standard	
1.				
2.				
3.				
e.t.c				
Name Excipient(s)				
1.				
2.				
3				
e.t.c				
Note: Only one name for each substance should be given in the following order of priority: INN, Pharmacopoeia, common name, scientific name.				
1.21	Name and address (physical and postal) of the Clinical Research Organisation(s) where the clinical studies of the product were conducted.			
Name: Company name:				

Address:

Country:

Telephone:

E-Mail:

2.0 DECLARATION BY AN APPLICANT

I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge.

I further confirm that the information referred to in my application dossier is available for verification during GMP inspection.

I also agree that I shall carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports to TFDA.

It is hereby confirmed that fees will be paid/have been paid according to the national/Community rules\*

Name: .....  
.....

Position in the company:  
.....

Signature:  
.....

Date:.....

Official stamp:.....

\* Note: If fees have been paid, attach proof of payment

## **ANNEX II: SUMMARY OF PRODUCT CHARACTERISTICS**

### **1. NAME OF THE IMMUNOLOGICAL VETERINARY PRODUCT**

{(Invented) name of immunological veterinary product strength and dosage form  
<target species>}

### **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

**Active substance<s>:**

**<Adjuvant(s):>**

**<Excipient(s):>**

For a full list of excipients, see section 6.1.

### **3. DOSAGE FORM**

### **4. CLINICAL PARTICULARS**

#### **4.1 Target species**

#### **4.2 Indications for use, specifying the target species**

#### **4.3 Contraindications**

<None>

<Do not use in...>

<Do not use in case of hypersensitivity to the active substance(s) <, to the adjuvant(s)> or to any of the excipient(s).>

#### **4.4 Special warnings <for each target species>**

<None.>

#### **4.5 Special precautions for use**

##### **Special precautions for use in animals**

<Not applicable.>

<Vaccinated {species} may excrete the vaccine strain up to {x days/weeks} following vaccination. During this time, the contact of immunodepressed and unvaccinated {species} with vaccinated {species} should be avoided.>

<The strain can spread to {species}.

Special precautions should be taken to avoid spreading of the vaccine strain to {species}.>

<Appropriate veterinary and husbandry measures should be taken to avoid spread to susceptible species.>

<{Species} and unvaccinated {species} in contact with vaccinated {species} may react to the vaccine strain, presenting clinical signs such as ....>

##### **Special precautions to be taken by the person administering the immunological veterinary product to animals**

<Not applicable.>

<In case of accidental <self-administration> <self-injection> <ingestion> <spillage onto skin>, seek medical advice immediately and show the package leaflet or the label to the physician.>

<People with known hypersensitivity to {INN} should <avoid contact with the veterinary medicinal product.> < administer the product with caution.>

<Personal protective equipment consisting of {specify} should be worn when handling the veterinary medicinal product.>

<The product should not be administered by pregnant women.>

<The vaccine can be pathogenic for humans. Since this vaccine has been prepared with live, attenuated microorganisms, appropriate measures should be taken to prevent contamination of the handler and other people that collaborate in the process.>



<Vaccinated {species} may excrete the vaccine strain up to {x days/weeks} following vaccination. Immunocompromised persons are advised to avoid contact with the vaccine and vaccinated animals during {period}.>

<The vaccine strain can be found in the environment for up to {x days/weeks}. Personnel involved in attending vaccinated {species} should follow general hygiene principles (changing clothes, wearing gloves, cleaning and disinfection of boots) and take particular care in handling litter from recently vaccinated {species}.>

<To the user:

This product contains mineral oil. Accidental injection/self injection may result in severe pain

and swelling, particularly if injected into a joint or finger, and in rare cases could result in the loss of the affected finger if prompt medical attention is not given.

If you are accidentally injected with this product, seek prompt medical advice even if only a very small amount is injected and take the package leaflet with you.

If pain persists for more than 12 hours after medical examination, seek medical advice again.

To the physician:

This product contains mineral oil. Even if small amounts have been injected, accidental injection with this product can cause intense swelling, which may, for example, result in ischaemic necrosis and even the loss of a digit. Expert, PROMPT, surgical attention is required and may necessitate early incision and irrigation of the injected area, especially where there is involvement of finger pulp or tendon.>

<The long-term effects of the product on the population dynamics of dung beetles have not been investigated. Therefore, it is advisable not to treat animals on the same pasture every season.>

#### **4.6 Adverse reactions (frequency and seriousness)**

#### **4.7 Use during pregnancy, lactation or lay**

<The safety of the veterinary medicinal product has not been established during <pregnancy><lactation> <lay>.>

<Pregnancy:>

<Can be used during pregnancy.>

<The use is not recommended (during the whole or part of the pregnancy).>

<Do not use (during the whole or part of the pregnancy).>

<The use is not recommended during <pregnancy> <lactation>.>

<Use only accordingly to the benefit/risk assessment by the responsible veterinarian.>

<Laboratory studies in {species} have not produced any evidence of a teratogenic, foetotoxic, maternotoxic effects.>

<Laboratory studies in <species> have shown evidence of teratogenic, foetotoxic, maternotoxic effects.>

<Lactation:>

<Not applicable.>

<Laying birds:>

<Do not use in birds in lay <breeding birds> and/or within 4 weeks before the onset of the laying period.>

<Fertility:>

<Do not use in breeding animals.>

#### **4.8 Interaction with medicinal products and other forms of interaction**

<None known.>

<No data available.>

<No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis.>

<Safety <and> efficacy data are available which demonstrate that this vaccine can be administered on the same day but not mixed with {description of tested product(s).} >

<Safety <and> efficacy data are available which demonstrate that this vaccine can be administered at least {X number of} <days> <weeks> <before> <after> the administration of {description of tested product(s).} >

<No information is available on the safety and efficacy of this vaccine when used at with any other veterinary medicinal product except the products mentioned above. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis.>

#### **4.9 Amounts to be administered and administration route**

<The vaccine should not be used if {description of the visible signs of deterioration}.>

#### **4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary**

#### **4.11 Withdrawal period(s)**

<Not applicable.>

<Zero days.>

<Meat and offal> <Milk> <Eggs>: {X} <hours> <days>

<{Degree days}>

<Not authorised for use in lactating animals producing milk for human consumption.>

<Do not use in pregnant animals which are intended to produce milk for human consumption within {X} months of expected parturition.>

<Not authorised for use in laying birds producing eggs for human consumption.>

<Do not use within {X} weeks of onset of the laying.>

### **5. IMMUNOLOGICAL> PROPERTIES**

Pharmacotherapeutic group: {group}, ATCvet code: {lowest available level (e.g. subgroup for chemical substance)}

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

### **6.2 Incompatibilities**

<Not applicable.>

<In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.>

<Do not mix with any other veterinary medicinal product <, except diluent or other component <recommended> <supplied> for use with the product>.>

<Safety <and> efficacy data are available which demonstrate that this vaccine can be mixed and administered with {description of tested product(s).} >

<None known.>

### **6.3 Shelf life**

<Shelf-life of the veterinary medicinal product as packaged for sale>

<Shelf-life after first opening the immediate packaging >

<Shelf-life after dilution or reconstitution according to directions >

<Shelf life after incorporation into meal or pelleted feed>

<6 months> <...> <1 year> <18 months> <2 years> <30 months> <3 years>

### **6.4 Special precautions for storage**

<Do not store above <25 °C> <30 °C>>

<Store below <25 °C> <30 °C>>

<Store in a refrigerator (2 °C – 8 °C)>

<Store and transport refrigerated (2 °C – 8 °C)>\*

<Store in a freezer {temperature range}>

<Store and transport frozen {temperature range}>\*\*

<Do not <refrigerate> <or> <freeze>>

<Protect from light>

### **6.5 Nature and composition of immediate packaging**

<Not all pack sizes may be marketed.>

### **6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products**

<Not applicable.>

<Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.>

<Dispose of waste material by boiling, incineration or immersion in an appropriate disinfectant approved for use by the competent authorities.>

<{Invented name} should not enter water courses as this may be dangerous for fish and other aquatic organisms.>

## **7. MARKETING AUTHORISATION HOLDER**

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

## **8. MARKETING AUTHORISATION NUMBER(S)**

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

<{DD/MM/YYYY}> <{DD month YYYY}>...

## **10. DATE OF REVISION OF THE TEXT**

{MM/YYYY} or <month YYYY>

<Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu/>.>

## **11. PROHIBITION OF SALE, SUPPLY AND/OR USE**

<Not applicable.>

<The import, sale, supply and/or use of {invented name} is or may be prohibited in certain Member States on the whole or part of their territory pursuant to national animal health policy. Any person intending to import, sell, supply and/or use <invented name> must consult the relevant Member State's competent authority on the current vaccination policies prior to the import, sale, supply and/or use.>

<Consideration should be given to official guidance on the incorporation of medicated premixes in final feeds.>

## **ANNEX III: CONTAINER LABELLING**

### **Primary packaging and where applicable secondary packaging label**

Every immediate and outer container of any medicinal product shall be labelled in clearly legible indelible letters in Kiswahili or English or both.

The immediate and where available the outer container packaging label shall include at least the following:

- (a) The name of the IVP.
- (b) Method of administration.
- (c) A list of active substance(s) (using INNs if applicable) showing the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume.
- (d) Indication(s) and recommended dosage per target species where practicable.
- (e) The batch number assigned by the manufacturer.
- (f) The manufacturing and expiry dates.
- (g) Storage conditions or handling precautions that may be necessary.
- (h) Directions for use and any warnings or precautions that may be necessary.
- (i) For Animal use only.
- (j) Withdrawal period if applicable.
- (k) The name and address of the manufacturer.
- (l) The name and address of the company or person responsible for placing the product on the market if different from the manufacturer.
- (m) Tanzania registration number (to be included after approval).
- (n) Forensic category.

For containers of less than or equal to 10 ml capacity that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container need only contain items (a), (b), (c), (e), (f), (g), (i), (j) and (k) — or a logo that unambiguously identifies the company and the name of the dosage form or the route of administration.

### **Small packs container**

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

- (a) Name, strength and pharmaceutical form of the IVP.
- (b) Name of the manufacturer.
- (c) The batch number assigned by the manufacturer.
- (d) The manufacturing and expiry dates.

## **ANNEX IV: INFORMATION LEAFLET**

### **1. Name of the veterinary medicinal product**

{(invented name) of product strength pharmaceutical form <target animal species>}

### **2. Forensic category**

State the proposed forensic category of the product.

### **3. Qualitative and quantitative composition**

#### **Active Immunogenic substance<s>:**

**<Adjuvant(s):>**

**<Excipient(s) if applicable:>**

The qualitative and quantitative composition should be stated for the active Immunogenic substance(s) and those excipients, where the knowledge is essential for the safe administration of the medicinal product. For example, preservatives should always be mentioned with their « E » numbers. Other excipients should not be mentioned here.

#### **3.1 Qualitative composition**

The international non-proprietary name (INN) should be used, accompanied by its salt, derivative or hydrate form if relevant. If no INN exists, the Pharmacopoeia name should be used. If the substance is not in the Pharmacopoeia, the usual common name should be used. In the absence of a common name, the exact scientific designation should be given. Substances without an INN or an exact scientific designation should be described by a statement of how and from what they were prepared. References to a pharmacopoeial quality should not be included.

Where the active substance is present in the form of the parent molecule, the standard terminology should be used (e.g. dexamethasone, levamisole).

Where the active substance is present as a salt, derivative or hydrate, this should be clearly stated e.g.: dexamethasone acetate, levamisole hydrochloride.

#### **3.2 Quantitative composition**

The quantity of the active substance must be expressed per dosage, per unit volume, or per unit of weight.

It is recommended that a visual description of the appearance of the product (e.g. colour, markings, clarity, and shape) or other parameters such as pH should be given.

Examples:

- Tablet – “White, circular flat bevelled-edge tablets marked ‘100’ on one side”.
- Solution for injection – “Pale yellow, clear solution for injection, pH 7.0”

If the product is not presented in the final pharmaceutical form intended for administration to animals, the final pharmaceutical form should also be stated, e.g. “powder and solvent for solution for injection”.

In case of tablets, designed with a score line, a statement should be given whether or not reproducible halving of the tablets has been shown.

Examples:

- “The tablets can be divided into equal halves”.
- “The score line is intended to facilitate ease of swallowing and not to divide

into equal doses”.

#### **4. Clinical particulars**

##### **4.1 Target species**

The target species, and sub-category, when appropriate, should be indicated.

##### **4.2 Indications for use, specifying the target species**

The indications should be clearly defined for the target species. It should be clearly stated whether the treatment is for prophylactic, therapeutic or diagnostic purposes.

##### **4.3 Contraindications**

<None>

<Do not use in...>

<Do not use in case of hypersensitivity to the active substance(s) <, to the adjuvant(s)> or to any of the excipient(s).>

##### **4.4 Special warnings for each target species**

The purpose of this section is to provide clear information on how to ensure the effective use of the product in target animals. Information could include recommendations on the handling of animals, the proper use of the product or any other impact on the efficacy of the product.

##### **4.5 Special precautions for use**

###### **4.5.1 Special precautions for use in animals**

The purpose of this section is to provide clear information on how to ensure the safe use of the product in animals. The section should include information on relative contraindications.

###### **4.5.2 Special precautions to be taken by the person administering the medicinal product to animals**

Risks resulting from the nature of the product, its preparation and use and of any risks resulting from the particular characteristics of the user should be stated here.

Possible hypersensitivity reactions in the user to any of the excipients or residues from the manufacturing process should be included.

###### **4.5.3 Other precautions**

Information should be included here regarding possible reactions of the product with its surrounding, e.g. impact on the environment or chemical reactions of the product with furniture or cloth.

Examples:

The solvent in this product may stain certain materials including leather, fabrics, plastics and finished surfaces. Allow the application site to dry before permitting contact with such materials.

This product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition. ... should not be allowed to enter surface waters as it has harmful effects on aquatic organisms.

Do not allow treated animals to swim in water courses until at least ...hours/days after administration.

“The long-term effects of YY on the population dynamics of dung beetles have not been investigated. Therefore, it is advisable not to treat animals on the same pasture every season”

#### **4.6 Adverse reactions**

Adverse reactions which have been described for the active ingredient(s) or their pharmacological class and which are very rare or occur with delayed onset of clinical signs. These reactions may not have been observed in relation to the product, but are generally accepted as being attributable to the pharmacological class. The fact that this is a class attribution should be mentioned

#### **4.7 Use during pregnancy, lactation or lay**

In order to ensure the safe use of the product, the user must be informed of the recommendations regarding the use of the product in pregnant/lactating animals or laying birds.

#### **4.8 Interaction with other medicinal products and other forms of interaction**

<None known.>

<No data available.>

<No information is available on the safety and efficacy of this vaccine when used with any other veterinary medicinal product. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis.>

<Safety <and> efficacy data are available which demonstrate that this vaccine can be administered on the same day but not mixed with {description of tested product(s).} >

<Safety <and> efficacy data are available which demonstrate that this vaccine can be administered at least {X number of} <days> <weeks> <before> <after> the administration of {description of tested product(s).} >

<No information is available on the safety and efficacy of this vaccine when used at with any other veterinary medicinal product except the products mentioned above. A decision to use this vaccine before or after any other veterinary medicinal product therefore needs to be decided on a case by case basis.>

#### **4.9 Amount(s) to be administered and administration route**



< Dosage to be given per each specified species and route of administration should be stated }.>

#### **4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary**

- "Signs as <description> may occur in <target species> when the dose is exceeded. "Do not exceed the recommended dose". (Effects which do not occur under normal treatment). And provide corrective measure if available

#### **4.11 Withdrawal period(s) if applicable**

<Not applicable.>

<Zero days.>

<Meat and offal> <Milk> <Eggs>: {X} <hours> <days>

<{Degree days}>

<Not authorised for use in lactating animals producing milk for human consumption.>

<Do not use in pregnant animals which are intended to produce milk for human consumption within {X} months of expected parturition.>

<Not authorised for use in laying birds producing eggs for human consumption.>

<Do not use within {X} weeks of onset of the laying.>

### **5. Pharmacological properties**

The section should begin by stating the therapeutic group, according to the ATCvet classification system and the group of substances to which it belongs (ATCvet code).

#### **5.1 Pharmacodynamic properties**

The pharmacodynamic activity of the active substance(s) should be specified, together with the mechanism of the action, on the basis of the information contained in the application dossier. Also, information on resistance should be included in this section, if appropriate.

#### **5.2 Pharmacokinetic particulars**

Information, relevant for the proposed use of the product should be provided on the absorption, distribution, biotransformation and excretion of the active substance in each of the target species.

#### **5.3 Environmental properties**

For products, which might enter the environment directly e.g. medicines for fish or via manure, general information on environmental effects should be provided. The impact of the active substance or relevant metabolites excreted into the environment should be addressed. Information on degradation and factors influencing this (e.g. light, pH, temperature) and other ways of deactivation (e.g. binding to organic

matter) should be given. Possible accumulation in the environment should be addressed.

## **6. Pharmaceutical particulars**

### **6.1 List of excipients**

A list should be given of the excipients, expressed qualitatively only. All excipients, which are present in the product, even those present in small amounts, should be included.

In the case of premixes for medicated feeding-stuffs, the main carriers in brackets should be indicated.

### **6.2 Incompatibilities**

Where incompatibility studies have not been carried out, and if appropriate for the product, a warning should be included <not to mix the product with other medicinal products> (e.g. for parenterals or premixes for medicated feeding stuffs).

In other cases, the standard term <None known> is used.

If incompatibility is not a concern due to pharmaceutical form of the product, e.g. solid oral pharmaceutical forms, the term used is <Not applicable>.

### **6.3 Shelf-life**

<Shelf-life of the veterinary medicinal product as packaged for sale>

<Shelf-life after first opening the immediate packaging >

<Shelf-life after dilution or reconstitution according to directions >

<Shelf life after incorporation into meal or pelleted feed>

<6 months> <...> <1 year> <18 months> <2 years> <30 months> <3 years>

### **6.6 Special precautions for the disposal of unused veterinary medicinal product or waste materials derived from the use of such products, if appropriate**

This section should include information necessary for the safe disposal of unused product, and the equipment used for the administration of the product to animals. In addition, reference should be made to any restrictions on the disposal of waste products from treated animals.

## **7. Registrant (Market Authorization Holder)**

State the name and address of registration holder including telephone, fax number and e-mail.

## **8. Date of revision of the text**

To be stated at the time of printing once a change to the prescribing information has been approved

## **ANNEX V: QUALITY OVERALL SUMMARY-(QOS)**

### **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 fulfill the same purpose.

Please state the exact location (Annex number) of any appended documents in the relevant sections of the form.

See sections 1.5, 3 and 4 of “Guideline on submission of documentation for registration of immunological veterinary pharmaceutical product (IVP): quality part” for general and detailed instructions on the completion of this template

Should you have any questions regarding this form, please contact the Tanzania Food and Drugs Authority (TFDA).

### **2.3. S Immunogenic substance (name, manufacturer)**

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

##### 2.3. S.1.1 Nomenclature

- (a) WHO or Pharmacopoeal name(s)
- (b) Biological name
- (c) For combination vaccines (names of immunogenic substances)
- (d) Chemical modification/conjugation of the immunogenic substance

2.3. S.1.2 Structure

- (a) Structural formula
- (b) Schematic amino acids sequence/molecular formula
- (c) Relative molecular mass

2.3.S.1.3 Physicochemical Characterization and Biological Activity

3.2.S.1.3.1 Physicochemical Characterization

3.2.S.1.3.2 Biological Activity

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

2.3.S.1.5 General description of the raw materials

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

**2.3. S.2 Manufacture of the immunogenic substance (name, Manufacturer)**

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 Immunogenic substance manufacturing process

- (a) Flow diagram of manufacturing process
- (b) Narrative description of the manufacturing process (es)
- (c) In process holding steps
- (d) Description of lot identification system
- (e) Description and validation of the inactivation or detoxification process
- (f) Description of the purification process
- (g) Description of the conjugation process
  
- (h) Stabilization of the immunogenic substance
  
- (i) Reprocessing (if applicable)

- (j) Filling Procedure

#### 2.3. S.2.3 Control of critical steps and intermediates

- (a) Critical steps in the process and controls performed
- (b) Description of sampling procedures

#### **2.3.S.2.4 Process Validation and/or evaluation**

#### **2.3. S.3 Characterization of the immunogenic substance**

- (a) Details of analytical testing
- (b) Impurities
  - (i) Product related Impurities
  - (ii) Process related Impurities

#### **2.3. S.4 Control of the Immunogenic Substance**

##### 2.3. S.4.1 Specifications

##### 2.3. S.4.2 Description of Analytical Procedures

##### 2.3. S.4.3 Analytical Method validation

##### 2.3. S.4.4 Batch analysis and Production consistency

##### 2.3. S.4.5 Justification of the quality specifications

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

- (a) Source (including lot number) of primary reference standards or reference materials  
(e.g. Ph.Int., Ph.Eur., BP, USP, in-house)
- (b) Characterization and evaluation of non-official (e.g. not from an officially recognized pharmacopoeia) primary reference standards or reference materials  
(e.g. elucidation of structure, certificate of analysis)
- (c) Description of the process controls of the secondary reference standard  
(comparative certificate of analysis and IR spectra against primary standard)

#### **2.3. S.6 Packaging and container closure system of the immunogenic substance**

#### **2.3. S.7 Stability of the immunogenic substance**

- (a) Stability Studies Protocol
- (b) Stability program or stability commitment
- (c) Stability data
- (d) Stability studies conclusion and proposed storage and transportation

conditions

**2.3. P FINISHED IMMUNOGENIC PRODUCT (NAME, MANUFACTURER)**

**2.3. P.1 Description and Composition**

- (a) Description of the finished immunogenic product
- (b) 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 appropriate title							
Subtotal 2							
Total							

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

**2.3. P.2 Pharmaceutical Development**

2.3. P.2.1 Compatibility of Immunogenic Substance with other components

2.3. P.2.2 Adjuvant, preservative, stabilizers, and excipients

2.3. P.2.3 Development of the manufacturing process

2.3. P.2.4 Container closure system

**2.3. P.3 Manufacture processes of the finished immunogenic product**

2.3. P.3.1 Manufacturer(s)

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

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

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

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

### 2.3. P.3.2 Batch Formula

Largest intended commercial lot size:

Other intended commercial lot sizes:

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

### 2.3. P.3.3 Description of the manufacturing process

(a) Flow diagram of the manufacturing process

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

### 2.3. P.3.4 Controls of Critical Steps and Intermediates

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

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

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

### 2.3. P.3.6 Description of the batch identification system

## **2.3. P.4 Control of the adjuvant, preservative, stabilizers, and excipients**

### 2.3. P.4.1 Specifications

(a) Summary of the specifications

### 2.3. P.4.2 Analytical Procedures

Summary of the analytical procedures for supplementary tests

### 2.3. P.4.3 Validation of Analytical Procedures

(a) Summary of the validation information for the analytical procedures for

supplementary tests (where applicable)

2.3. P.4.4 Justification of Specifications

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

2.3. P.4.5 Excipients of Human or Animal Origin

- (a) For FPPs using excipients *without* risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:
- (b) CEP(s) demonstrating TSE-compliance can be found in:

2.3. P.4.6 Novel Excipients

**2.3. P.5 Control of finished immunogenic product**

2.3. P.5.1 Specifications of the immunogenic product

2.3. P.5.2 Analytical Procedures

- (a) Summary or references to analytical procedures

2.3. P.5.3 Validation of Analytical Procedures

- (a) Summary or references to the validation information

2.3. P.5.4. Lot consistency and analysis

- (a) Description of the lots:

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

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

2.3. P.5.6 Justification of Specification(s)

3.2. P.5.7 Analytical certificates

**2.3. P.6 Reference Standards or Materials**

- (a) Source (including lot number) of primary reference standards or reference



materials (e.g. Ph.Int., Ph.Eur., BP, USP, in-house)

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

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

**2.3. P.7 Container Closure System**

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

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

**2.3. P.8 Stability of the Finished Immunogenic Product**

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

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

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

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

Container closure system	Storage statement	Shelf-life

2.3. P.8.2 Post-approval stability program

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

2.3. P.8.3 Stability Data

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

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