Botswana Medicines Regulatory Authority

MEDICINES REGULATORY AUTHORITY

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1. Purpose

The guideline provides for the format and content of applications for registration of immunological veterinary medicinal products. It is intended to assist applicants to generate and compile a Common Technical Document for application to register vaccines and other immunologicals with Botswana Medicines Regulatory Authority (BOMRA).

2. Scope

This guideline applies to all immunological veterinary medicinal products registration applications containing existing APIs of synthetic or semi-synthetic origin.

3. Abbreviations and Definitions

3.1 Abbreviations

For the purposes of this guidance document, the following abbreviations shall apply:

API	Active Pharmaceutical Ingredient (i.e. immunogenic substance/antigen)
API MF	Active Pharmaceutical Ingredient Master File
BCS	Biopharmaceutical Classification System
BMR	Batch Manufacturing Record
BOMRA	Botswana Medicines Regulatory Authority
BP vet	British Pharmacopoeia – Veterinary Medicines
BPR	Batch Packing Record
BSE	Bovine Spongiform Encephalopathy
BTIF	Bioequivalence Trial Information Form
CBER	Center for Biologics Evaluation and Research
CCS	Container Closure System
CEP	Certificate of Suitability (Ph Eur monograph)
cGMP	current Good Manufacturing Practices
CoA	Certificate of Analysis
CoPP	Certificate of Pharmaceutical Product
CQA	Critical Quality Attributes
CTD	Common Technical Document
CV	Curriculum Vitae
CVMP	Committee for Medicinal Product for Veterinary Use
DMF	Drug Master File
DPER	Department of Product Evaluations and Registrations
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
ELISA	Enzyme-Linked Immunosorbent Assay

EU	European Union
FDC	Fixed Dose Combination
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMO	Genetically Modified Organism
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
INN	International Non-proprietary Name
IVMP	Immunological veterinary medicinal product
JP	Japanese Pharmacopoeia
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MAP	Multiple Antigen Peptides
MCB	Master Cell Bank
MCS	Master Cell Seed
mRNA	Messenger Ribonucleic Acid
MRSA	Medicines and Related Substances Act
MS	Master seed
MSV	Master Seed Virus
NMRA	National Medicines Regulatory Authority (Also called NRA - National Regulatory Authority)
PCR	Polymerase Chain Reaction
PDF	portable document format
Ph. Eur.	European Pharmacopoeia
PI	Package Insert
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme
PIL	Patient Information Leaflet
PMF	Plasma Master File
PVC	Polyvinyl Chloride
QA	Quality Assurance
QIS	Quality Information Summary
QOS	Quality Overall Summary
QTPP	Quality Target Product Profile

rDNA	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
SADC	Southern African Development Community
SPC	Summary of Product Characteristics (European)
SPF	Specific Pathogen Free
TSE	Transmissible Spongiform Encephalopathy
USFDA	United States Food and Drugs Administration
USP	United States Pharmacopoeia
UV	Ultraviolet
VICH GL	VICH Guideline
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMP	Veterinary medicinal product
WCB	Working Cell Bank
WCS	Working Cell Seed
WHO	World Health Organisation
WS	Working Seed
WSV	Master Seed Virus

3.1 Definitions

For the purposes of this guidance document, the following definitions shall apply:

Active / Immunogenic Substance - Any substance/antigen or mixture of substances/antigens used in the manufacture of an immunological veterinary medicinal product (IVMP), and that, when so used, becomes an active ingredient/component of that IVMP. Such substances are intended to induce an immunologic response or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

Applicant- A company/entity registered, licensed or operating in Botswana that submit an application, in terms of the Act, for a registration or licensing to sell a medicinal product (Marketing Authorisation), an update or amendment to an existing marketing authorization. Once the marketing authorisation is granted, the applicant becomes the Marketing Authorisation Holder for that medicinal product.

Commitment batches - Production batches of an immunogenic substance or IVMP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

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

Finished product (usually written as FPP) - The formulated medicinal product containing the active ingredient(s) which has undergone all stages of manufacture, including packaging in its final container and labelling and ready for administration either alone or after reconstitution with the relevant diluents.

Reference product - is an originator/ innovator product, i.e. that product, which was either first to be authorised for marketing or accepted as a comparator product, on the basis of documentation of quality, safety and efficacy data.

Manufacturer - A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of the immunogenic substance or an IVMP.

Officially recognized pharmacopoeia - refers to the pharmacopoeia recognized internationally e.g. British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.), The International Pharmacopoeia (Ph. Int.), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP).

Ongoing stability study - The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the active (immunogenic) substance, or confirm or extend the shelf-life of the IVMP (sometimes called FPP).

Pilot-scale batch - A batch of an active (immunogenic) substance or IVMP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. Usually 10% of the production scale batch.

Primary batch - A batch of an active (immunogenic) substance or IVMP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life.

Production batch - A batch of an active (immunogenic) substance or IVMP manufactured at production scale by using production equipment in a production facility as specified in the application.

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.

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.

Immunological Medicinal 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 the ensure stability.

Working Seed - 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.

4. Introduction

In accordance with the provisions set out in the Medicines and Related Substances Act (MRSA) of 2013, and the Medicines and Related Substances Regulations of 2019, which were gazetted on the 27th of December 2019, the Botswana Medicines Regulatory Authority will open for submission of applications for registration of Veterinary medicinal Products with effect from xxx of August 2020. The approved fees for the regulatory services offered by BOMRA are appended at Schedule 5 (pages C.1168 to C.1177) of the said regulations. This guideline provides recommendations on the information to be included, and the format, IVMP dossiers for

submission to BOMRA. The Authority recommends the applicants to compile their IVMP registration applications in CTD format. It also, provides recommendations on the quality information for the active / immunogenic substances and the finished product, that is the IVMP, that should be submitted to support applications for registration. Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. Applicants should refer to appropriate VICH guidelines, Ph. Eur. Monographs and other EMA guidelines for detailed guidance on submission of efficacy and safety data to support applications for registration of new IVMPs.

4.1 Objective

This guideline is intended to,

4.1.1 Assist applicants in the preparation of the applications for registration by providing clear general guidance on the format and content of the applications

4.1.2 Fully adopt the modular format of the common technical document

4.1.3 Provide guidance on the technical and other general data requirements

These measures are intended to promote effective and efficient processes for development of applications for registration and the subsequent assessment procedures of IVMPs

4.2 General Principles

To facilitate the preparation of the applications, this guideline is organized in accordance with the structure of the Common Technical Document, as developed by ICH. The content of this guideline should be read in conjunction with the current MRSA, the Medicines and Related Substances Regulations and other relevant requirements described in other existing VICH or ICH and/or EMA's CVMP reference documents and guidelines. For those IVMPs intended for use in food producing animals, applicants are encouraged to ensure their inactive pharmaceutical ingredients are approved for use in food producing animals.

Scientific literature may be appropriate to fulfill the requirements for some of the information or parameters outlined in this guideline (e.g. qualification of specified identified impurities). Furthermore, the requirements outlined in certain sections may not be applicable for the proposed IVMPs. In these situations, a summary and the full reference to the scientific literature should be provided or the non-applicability of the requested information should be clearly indicated as such with an accompanying explanatory note.

4.3 Guidance on format

4.3.1 Preparing and Organising the Common Technical Document

To facilitate the review of the basic data and to help an evaluator become oriented with the application contents, the display of information should be unambiguous and transparent throughout the CTD. If additional or supplementary data are submitted, the module(s) should be identified, and numbering should follow the original documentation. The applicant should not submit the modules that are not used i.e. it is unnecessary to include "not applicable" pages against unused CTD headings. For new applications, detailed statements justifying the absence of data or specific CTD sections should be provided in the relevant Quality Overall Summary (QOS) and/or Non-Clinical/Clinical Overviews (Module 2.3, 2.4, 2.5). If relevant, justification for empty sections in Module 1 is to be provided in the cover letter. Acronyms and abbreviations should be defined the first time they are used in each module.

4.3.2 Documentation

4.3.2.1 Electronic review documents

Electronic documentation (on CDs) should be submitted in Microsoft Word (for required templates or summaries, e.g. QOS, QIS) and text-selectable PDF format (for all other documentation). Guidance on eCTD submissions will be provided in future.

4.4 Organising documents

Each section of the dossier is to be marked by use of clearly annotated tabs and the documentation should be filed in accessible files. Lever arch files are not acceptable. Documents can be combined in volumes as long as appropriately named tab identifiers separate them. For example, the Package Insert should be separated from the other documents by a tab identifier. In general, documents from different CTD modules should not be included in the same electronic folder.

Administrative documents (e.g. Application cover letter, application forms, screening checklists, manufacturing licences, cGMP certificates are included in Module 1. The organisation of such documents should be consistent with the structure described in this guideline. Since these administrative documents are small, they should be placed in the same electronic folder, separated by tab identifiers.

4.5 Folders / Files identification

Folders must be numbered by module, resulting in a separate set of numbers for each module. The labelling of each folder/file should include:

a) Name of applicant

b) Name of product, strength and dosage form

c) Module or folder/file number. The files in each module should be numbered separately and sequentially using the format: x of y files, where x is the number for the specific file and y is the total number of files submitted for the respective module, e.g. Module 3, File.1of 6.
d) Copy number: The copies of Modules 1, 2 and 3 should be numbered as copies x of y.
e) Contents. Each file must also be labelled according to the section(s)which it contains, e.g.:
Section 3.2.P.4 means:

3. –Module 3 - Qualities
2. – Body of data
P. – Product
4. – Control of excipients

4.6 Pagination

A document is a set of pages, numbered sequentially and divided from other documents by a tab. Page numbering should be at the document level and not module/file level. (The entire submission should never be numbered consecutively by page.) In general, all documents should have page numbers. Since the page numbering is at the document level, there should only be one set of page numbers for each document.
Cross-referencing to documents should be made by referring to the CTD module, volume, tab identifier, and page number (for example: *"see Module 3, Vol. 6, P.4.3 Method validation, p 23"*).

Those documents that are provided as hard copies (Application Forms), must be legible and margin space must be sufficient on both the left and right side, so that information is not obscured when the page is placed in a binder. However, Module 1.3 Labelling and packaging (1.3.1.1, 1.3.2, 1.3.3) must be copied single-sided. Copying of each document must start on a new page and must be separated from the next document by a tab.

4.7 Paper size

Standard A4 paper should be used for all submissions. Text and tables should be prepared using margins that allow the document to be printed on A4 paper. The left-hand margin should be sufficiently large that information is not obscured through binding (if printing is done).

4.8 Fonts

Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying or when provided electronically**.** *Arial/Times New Roman 12-point* font is preferred for narrative text, but printing in a font size with a legibility equivalent to at least Arial 10-point black on white could be used. The copies, including figures, tables and photos should be clearly legible. Shading and/or coloured filling/background and/or print, e.g. in tables and headers, or across pages, is unacceptable and should be avoided.

The recommendations outlined in this guideline for preparation of applications for registration in CTD format should be followed for the format and presentation of the application. There may be a

number of instances where repeated sections can be considered appropriate. Whenever a section is repeated, it should be made clear what the section refers to, by creating a distinguishing title in parentheses following the M4Q (CTD-Q) guideline heading, e.g. 3.2.S Drug substance (or API) (name, Manufacturer A).

The following are recommendations for the presentation of the information in the Quality Module for different scenarios that may be encountered.
a) The Open part (non-proprietary information) of each APIMF should always be included in its entirety in the application, as an annex to 3.2.S.
b) for an IVMP containing more than one active/immunogenic substance: one complete "3.2.S" section should be provided for one API, followed by other complete "3.2.S" sections for each other API.
c) for an active/immunogenic substance from multiple manufacturers: one complete "3.2.S" section should be provided for the active/immunogenic substance from one manufacturer, followed by other complete "3.2.S" sections for each other active/immunogenic substance manufacturer.
d) for an FPP with multiple container closure systems (e.g. bottles and unit dose blisters): one complete "3.2.P" section should be provided with the information for the different presentations provided within the subsections.
e) for multiple IVMPs (e.g. solution and lyophilised powder): a separate dossier is required for each IVMP.
f) for an IVMP supplied with reconstitution diluent(s), one complete "3.2.P" section should be provided for the Finished product, followed by the information on the diluent(s) in a separate part "3.2.P", as appropriate.

For more information on when one or separate applications are required, applicants should refer to section 1.4.1 to 1.4.4 in Module 1 below.

4.9 Scheduling of VMPs

The proposed categories for distribution / classification of VMP as given in the proposed amendments to the Act) are as follows,

- **Schedule 1 medicine:** a medicine which is highly addictive and therefore liable to abuse, subject to strict storage, dispensing, destruction and record-keeping requirements and may be dispensed only on written prescription, which prescription must be kept by the dispensing pharmacist or veterinary surgeon for a minimum of 5 years
- **Schedule 2 medicine** - a medicine which is less liable to abuse than Schedule 1 and which must be kept under locked storage
- **Schedule 3 medicine** - a medicine which is less liable to abuse and does not have strict storage requirements but is subject to normal storage requirements

- **Schedule 4 medicine** - a medicines which are very low preparations of codeine containing products that are exempt from all controlled drug requirements
- **Precursors:** likely used to produce psychotropics/narcotics
- **POM:** Prescription Only Medicine - a pharmaceutical, biological/ immunological, complementary product, not containing narcotic or psychotropic substances, which is dispensed by a pharmacist under a prescription issued by a registered veterinary surgeon or by a veterinary surgeon from their own stock to treat animals under their care.
- **VPS:** Veterinary, paraprofessional - a pharmaceutical, biological/ immunological, complementary product not containing narcotic or psychotropic substances which are dispensed by a pharmacist under prescription issued by a registered veterinary surgeon or veterinary paraprofessional or by a registered veterinary surgeon or registered paraprofessionals in authorized premises. Supply of a prescription from veterinarian or a veterinary paraprofessional is required.
- **General Sales Medicines:** a pharmaceutical, biological/ immunological, complementary product not containing narcotic or psychotropic substances which is sold without prescription in authorized premises. No prescription is required for these medicines.

CTD MODULES 1-5
Numbering and labelling of folders and files should be done following the CTD format.

Module 1: ADMINISTRATIVE INFORMATION

This module contains all administrative information or documents, for example, general correspondence, application forms, certifications, labelling and annexures as needed. The documents should be organised in the order listed below.

1.1 ***Motivation/Cover letter*** (covering the details specified below)
Should be submitted with the product dossier by the responsible person *(on behalf of applicant)* highlighting the,

- Name of product
- Name of active/immunogenic substance(s)
- Target species
- Strength, formulation, route & method of administration, description of pack sizes.

The same letter should briefly indicate why the product should be considered for registration in Botswana and provide the contact details (postal address, tele- & cell phone numbers and e-mail) of the person to whom all correspondences should be directed.

1.2 ***Proof of payment*** of relevant application fees
Applicants should consult the current fee schedule for the correct and appropriate application fee for registration of immunological veterinary medicinal products. A copy of the invoice or proof of

payment of the application fees should be submitted. Unless a full application fee is received, the application will not be accepted into the system.

If payment is made through the bank, all costs of payments, transfer charges or commissions charged by the bank, are borne by the applicant. You are further advised to clearly specify, in your instructions to the bank, that such payment is "Application fee for registration of Product xxxxx" to avoid unnecessary delays during which the Authority tries to identify your payment from a pool of some unallocated funds. [Medicines and Related Substances Regulations of 2019, gazetted on the 27th of December 2019, Schedule 5 (page C.1176)]

1.3 Comprehensive table of Contents

A comprehensive table of contents shall indicate the sections, subsections and corresponding page numbers for the whole application

1.4 Application Form

A completed signed and dated application form should be submitted for each IVMP. All forms are to be completed in English. The application form should be downloaded from BoMRA website www.bomra.co.bw. An application not submitted in the appropriate format, incomplete or illegible will be rejected. An application for registration of a veterinary medicinal product may be made by:

- The prospective holder of the marketing authorization/registration, hereinafter referred to as the applicant
- If the applicant is not a manufacturer, the applicant must submit evidence of empowerment of power of attorney.

Annexes to the application form includes:

a. Proof of payment
b. Letter of authorisation for communication on behalf of the applicant
c. Electronic copy of declaration
d. CV of the qualified expert (s) for pharmacovigilance
e. CEP where available
f. Evidence of registration in the country of origin (certificate of registration/Marketing authorisation)
g. Letter of access from the API MF holder or CEP holder,
h. QIS

Consider the following to determine what constitute a single application or two separate applications.

1.4.1 Solid Dosage Formulation (Tablets, Capsules, Suppositories, Boluses)

1.4.1.1 Different pack sizes for the same strength and formulation require one application

1.4.1.2 Different strength and / or formulation requires separate applications

1.4.2 Liquids (Syrups/suspensions/solutions)

1.4.2.1 Different containers of the same strength and formulation will require one application

1.4.2.2 Same container size of different strength and/or formulation will require separate applications

1.4.3 Injectable Liquids and Powders (Ampoules, vials, Prefilled Syringes (PFS), or large volume parenteral)

1.4.3.1 Ampoules containing parenteral preparations of different strength and formulation will require separate applications,

1.4.3.2 Ampoules containing identical parenteral preparations of the same strength and/or formulation, but different volumes will require separate applications,

1.4.3.3 Ampoules and/or single dose vials containing dry powder, crystals etc of different mass will require separate applications,

1.4.3.4 Dry powders or crystals etc. of the same respective mass, packaged in ampoules and single dose vials will require separate applications,

1.4.3.5 Ampoules, single dose vials, as well as disposable syringes and cartridges containing identical parenteral preparations of the same strength and same volume of liquid will require one application,

1.4.3.6 Ampoules containing "water for injection", but of different volume will require one application,

1.4.3.7 Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection, will require one application,

1.4.3.8 Ampoules containing identical parenteral preparations of different volumes used only as a diluent in the reconstitution of a preparation for parenteral use, will require separate applications,

1.4.3.9 Multi-dose vials of the same strength and formulation in different volumes will require separate applications,

1.4.3.10 Multi-dose vials and a single dose ampoule of the same formulation will require separate applications,

1.4.3.11 Multi-dose vials containing dry powder of different mass and the same formulation, and having the same concentration when reconstituted will require one application,

1.4.3.12 A container of diluent to be used with any preparation in (iii), (iv) or (xii) will require one application provided that the diluent is also fully described in the dossier together with the product,

1.4.3.13 An ampoule of diluent to be used with any biological preparation will require one application,

1.4.3.14 Infusions of the different volumes and of the same formulation, which are packed in containers of exactly the same type of material, will require separate applications,

1.4.3.15 Infusions of the same or different volumes and of the same formulation, which are packed in containers made of different types of materials, will require separate applications,

1.4.3.16 A preparation, packed in plastic containers and intended also to be marketed in glass containers containing the same volume and the same formulation, will require one application provided the following comparative data are submitted: -

a) Characteristics of the rubber stopper,
b) Specifications for the glass,
c) A comprehensive manufacturing process with particular reference to the washing and sterilization cycles and apparatus used,
d) Data on particulate matter (contamination),
e) Stability data with reference to the effect of the pH of the parenteral liquids.

1.4.3.17 Products with the same strength and formulation but with different colours and/or flavours will require separate applications,

1.4.3.18 Applications containing the same active ingredient(s), and where additional indications are sought, where such new indications render the product in a different scheduling status, or different pharmacological classification or have any other restrictions imposed other than the original application, will require separate registration.

1.4.4 Applicants/Proprietary names

1.4.4.1 Same formulation applied under different proprietary names will require separate applications

1.4.4.2 Same formulation from different applicants will require separate applications

1.5 Declaration by the applicant

A declaration attesting the accuracy of the contents of the application should be made by the applicant or responsible person nominated by the applicant. The responsible person should be one who is qualified by way of requisite skills and professional qualifications. Any misleading or false declarations may lead to prosecution.

1.6 Screening Checklist

The applicant should complete a screening checklist. This document will be assessed by the Authority upon submission of the application to determine completeness of the application prior to it being accepted into the system. All applications deemed incomplete will be rejected and the applicant will be requested to re-submit a complete application. A new screening fee will be payable on resubmission of applications that would have failed initial screening.

1.7 Product Specific Data Composition

Based on the type of product, the application for registration of IVMPs should be compiled in accordance with the guidance given below.

1.8 *Manufacturing and Marketing Authorisations* (Other international registrations obtained)

List all the countries in which applications for registration of the IVMP have been,

a) submitted and pending registration,
b) granted a marketing authorisation (copies of registration certificates/ marketing authorisation to be submitted),

c) rejected, deferred or cancelled marketing authorisation, and the reasons thereof.

If the product is not registered in the country of origin, reasons for non-registration should be provided. Further to that, registration in the country of manufacture should be disclosed. If not registered or if withdrawn, cancelled, suspended or revoked, the reasons for such, should be provided.

1.9 Good Manufacturing Practices

For all products, irrespective of the country of origin, it is expected that all key manufacturing steps of the active /immunogenic substance and finished products (IVMPs) are performed in plants or facilities that are compliant with cGMP. These facilities include, primary manufacturing sites, secondary manufacturing sites (packers), and quality control (batch release control) sites. The applicant should provide:

1.9.1 A list of the facilities and the date of last inspection of each site. Details should include name of facility, licence number, date of last inspection and inspecting Health Authority.

1.9.2 An inspection report not older than three years and / or latest cGMP certificate or cGMP compliance letter

1.10 SPC (Package inserts and information leaflets)

Copies of the SPC or package insert, and information leaflets in accordance with recognised regional and / or international format should be submitted. These should be legibly written in English and comprehensible. The proposed information leaflet should be written in layman's language (Basic English)

1.11 Labels

Labels should be prepared as per Botswana requirements, refer to the current version of the MRSA and its regulations. The applicant should submit a specimen or proposed artwork in colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging / labelling of the medicine. This can be a paper copy or computer-generated version.

NB. A specimen is a sample of the actual printed outer and inner packaging materials and package leaflet. If there are multiple strengths and/or pack sizes, all representative specimens or proposed artworks should be submitted. If the batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels, else the label should have provision for batch numbers, date of manufacture and / or expiry of the medicine.

1.12 Product samples

1.12.1 A single sample in each of the proposed packaging materials should be submitted for assessment of the label. More samples for testing may be requested as and when necessary/required.

1.12.2 A CoA of the finished product should be included. Ensure that the batch number on the CoA corresponds with the batch number on the sample.

Module 2: OVERVIEWS AND SUMMARIES

Module 2 of the CTD dossier contains the summaries and overviews for the quality, safety and efficacy sections of the Dossier. For innovator products, the clinical overview should include a statement regarding Good Clinical Practice (GCP) compliance.

2.1 Table of Contents for Module 2

The table of contents should detail the topics / headings and content covered in this module including the respective pagination

2.2 Introduction to CTD submission

The introduction should include proprietary name, non-proprietary name or common name of the active / immunogenic substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

2.2.1 Quality Overall Summary (QOS)

The Quality Overall Summary (QOS) template BOMRA/ER/VET/P02/F07 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. It should include sufficient information from each section to provide the Quality reviewer with an overview of Module 3.

The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed, a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies discussed under the CTD-S module), including cross-referencing to volumes and page numbers in other Modules.

The use of tables to summarize the information is encouraged, where possible. Other approaches to summarize the information can be used if they fulfil the same purpose. The QOS should be provided in both word and PDF version. The word version is a must. 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. All sections and fields in the QOS template that would be applicable should be completed following the guidance below.

2.2.2 Quality Information Summary (QIS)

The QIS template, BOMRA/ER/VET/P02/F08, should be completed to provide a condensed summary of the key quality information for the application for registration and constitutes part of the submission package. The QIS provides an accurate record of technical data in the application for registration at the time of registration. The QIS is a condensed version of the QOS and represents the final agreed upon key immunogenic substance and IVMP information from the assessment report (inter alia identification of the manufacturer(s)/site addresses, immunogenic substance and IVMP specifications, stability conclusions and relevant commitments).

The QIS template is structured according to the numbering and section headings of the ICH M4Q (CTD-Q) guideline to permit the rapid assembly of the QIS by copying requisite information from the corresponding portions of the QOS filed with the application for registration. It is acknowledged that the numbering of the sections in the QIS may not be entirely sequential. Those sections not considered necessary to be included in the QIS have been removed (e.g. 2.3.S.5 Reference standards or materials) and the remaining sections retain their numbering to be consistent with the original application for registration. The QIS serves as an official reference document in the course of GMP inspections, variation assessments and requalification assessments as performed by BoMRA. The QIS should always be amended as and when changes are made during the assessment process and it should be submitted with responses or variation applications.

2.2. S Active Substances

2.2. S.1 General Information

Information from 3.2.S.1 should be included

2.2. S.2 Manufacture (name, physical address)

A summary of the information from 3.2.S.2 should be provided. This includes:

- Information on the manufacturer,
- A brief description of the manufacturing process and the controls involved,
- A flow diagram, as provided in 3.2.S.2.2,
- A description of the source and Starting Material and raw materials of biological origin used in the manufacture of the active / immunogenic substance, as described in 3.2.S.2.3
- A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria, including critical process intermediates, as described in 3.2.S.2.4
- A description of process validation and/or evaluation, as described in 3.2.S.2.5
- A brief summary of major manufacturing changes made throughout development and conclusions from the assessment used to evaluate product consistency, as described in 3.2.S.2.6

NB. The QOS should also cross-refer to the non-clinical and clinical studies that used batches affected by these manufacturing changes, as provided in the CTD-S and CTD-E modules of the dossier

2.2. S.3 Characterisation of drug substance (name, manufacturer)
A summary of the interpretation of the evidence of structure, molecular and biological properties as described in 3.2.S.3.1 should be included. Data on potential and actual impurities arising from the manufacture and /or degradation including the basis for and qualification of set acceptance criteria/limits for individual and total impurities should be included.

2.2. S.4 Control of immunogenic substance (name, manufacturer)

Specifications from section 3.2.S.4.1 should be provided, including a brief summary of justification of the specifications, a summary of analytical procedures and validation. A tabulated summary of active/immunogenic batch analysis data as provided in section 3.2.S.4.4 should be provided.

2.2. S.5 Reference standards or Materials (name, manufacturer)

A tabulated summary of the information from section 3.2.S.5 should be provided

2.2. S.6 Container Closure System (name, manufacturer)

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

2.2. S.7 Stability (name, manufacturer)

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 as described in section 3.2.S.7.1.

A tabulated summary of the stability study results as provided in Section 3.2S.7.3 should be provided.

2.2. P. Immunological Veterinary Medicinal Products (name, dosage form)

2.2. P.1 Description and Composition of the drug Product (name, dosage form)

A summary of the description and composition of the veterinary product as provided in section 3.2.P.1 of the CTD dossier should be included

2.2. P.2 Pharmaceutical Development (name, dosage form)

A summary of the information from section 3.2.P.2 should be provided. This includes a tabulated summary of the composition of the formulations used in clinical trials (i.e. development work) and a presentation of dissolution profiles should be provided, where relevant.

2.2. P.3 Manufacture (name, dosage form)

Information from 3.2.P.3 should include:

- Information on the manufacturer
- A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality
- A flow diagram, as provided under 3.2.P.3.3
- A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5

2.2. P.4 Control of Excipients (name, dosage form)

A brief summary on the quality of excipients, as described in 3.2.P.4, should be included

2.2. P.5 Control of Finished Product (name, dosage form)

Include the specifications as provided in section 3.2.P.5.1 and a brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities. A tabulated summary of FPP batch analyses data as provided in section 3.2.P.5.4 should be provided.

2.2. P.6 Reference Standards or Materials (name, dosage form)
A tabulated presentation of the information from 3.2.P.6 should be provided

2.2. P.7 Container Closure System (name, dosage form)
A brief description and discussion of the information, from 3.2.P.7 should be provided

2.2. P.8 Stability (name, dosage form)
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 as described in section 3.2.P.8.1. A summary of the post-approval stability protocol should also be included. A tabulated summary of the stability study results as provided in Section 3.2P.8.3 should be provided

2.2. R. Regional Information

A brief description of the information specific for the region, as provided under "3.2.R" should be included, where appropriate.

2.2.3 Safety Overview

Module 4 of the dossier contains the non-clinical (pharmaco-toxicological) data relevant to the application. Generally, for well-known active pharmaceutical ingredients (generic medicines), submission of non-clinical overview may be exempted.

2.2.4 Efficacy Overview

Module 5 of the dossier contains the clinical data relevant to the application. Generally, for well-known active pharmaceutical ingredients (generic medicines), submission of clinical overview may be exempted.

2.2.5 Safety Written and Tabulated Summaries

Module 4 of the dossier contains the non-clinical (pharmaco-toxicological) data relevant to the application. Generally, for well-known active pharmaceutical ingredients (generic medicines), submission of non-clinical written and tabulated summaries may be exempted.

2.2.6 Efficacy Summary

Module 5 of the dossier contains the clinical data relevant to the application. Generally, for well-known active pharmaceutical ingredients (generic medicines), submission of clinical summary information may be exempted.

Module 3: QUALITY

3.1 Table of Content of Module 3

A table of content of the filed product dossier should be provided and it should be hyperlinked to the section of the dossier where the information is presented.

3.2 Body of data

3.2. S IMMUNOGENIC SUBSTANCE

The full information, from chemistry, manufacture, quality control during manufacture, process validation etc., for each of the immunologic substances in the IVMP, should be submitted in the dossier as outlined in the sections below. The quality overall summary in section 2.3 above, should be completed in accordance with the outline given below.

3.2. S.1 General Information

3.2. S.1.1 Nomenclature

(Bulk Antigen from WSV)

A full description of the immunogenic substance should be provided. The biological name (including strain and/or clone designation) or scientific name (strain and / or clone designation), including any established/approved name, should be provided. The description should also include the source of the cells and 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 other inactive/non-immunogenic substances, present in the immunogenic substance, should be provided.

3.2. S.1.2 Structure/ Characterisation of the immunogenic substances

The structural formula, the molecular formula, and the relative molecular mass should be provided where applicable. Information should generally include but should not be limited to the following:

- UV/visible or mass spectrometry
- amino acid analysis
- amino acid or nucleic acid sequencing
- carbohydrate analysis and, if appropriate, sequencing
- peptide mapping
- determination of disulphide linkages
- Sodium Dodecyl Sulphate-Polyacrylamide Gel Electrophoresis (SDS-PAGE) (reduced and non-reduced)
- isoelectric focusing (1D or 2D)
- nuclear magnetic resonance spectroscopy; and/or
    - assays to detect related proteins including deamidated, oxidized, processed, and aggregated forms and other variants, such as amino acid substitutions and adducts/derivatives, and other process contaminants such as sulfhydryl reagents, urea, residual host proteins, residual DNA, and endotoxin.

Additional physico-chemical characterization may be required for modified immunogenic substances such as conjugates, multiple antigen peptides (MAP), or those undergoing further chemical or

enzymatic modifications. The information provided should include the degree of derivatization or conjugation, the amount of unmodified substance, removal of free materials (e.g., toxins, linkers, etc.), and the stability of the modified immunogenic substance.

3.2. S.1. 3 General Properties: Biological Activity

Further characterization of the immunogenic substances may include, but not limited to the following:

- specific identity testing such as western blot analysis or ELISA
- cytometric analysis
- neurovirulence testing, if appropriate
- serotyping
- electrophoretic typing
- inactivation studies
- neutralization assays; and
- titrations.

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. A complete description of the protocol used for each bioassay, the control standards used, the validation of the inherent variability of the test, and the established acceptance limits for each assay should be provided. The characteristics of specific antibodies used in the immunochemical or serological assays should also be included.

Ref:

3.2. S.2 Manufacture of the immunogenic Substance(s)

(beginning at WS)

3.2. S.2.1 Manufacturer(s)

3.2. S.2.1.1 Identification

The name, address, and responsibility of the facilities involved in the manufacturing, packaging, labelling, and testing of the active/immunogenic substance should be provided.

The list of manufacturers should specify the actual physical addresses of the manufacturing site(s) involved, including block(s) and units(s), rather than the administrative offices. Telephone number(s), fax number(s) and email address (es) should be provided.

A valid certificate of GMP compliance and a valid manufacturing authorization or licence issued by the competent authority in the country of manufacture of the immunogenic substance should be provided.

3.2. S.2.2 Manufacturing Process

*[**ref: USFDA CBER** Guidance for Industry: Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product and,*

***Ph. Eur.** Monographs 0062, 5.2.3 and 5.2.4 and other disease specific monographs]*

The description of the manufacturing process for each immunogenic substance represents the applicant's commitment to the manufacture of the immunogenic substance. A detailed description of the manufacturing process and respective controls should be provided to demonstrate proper quality control and prevention of possible contamination with adventitious agents or any other active substance/products in the facility. Alternate processes, if any, should be explained and described with the same level of detail as the primary process. It should be demonstrated that batches obtained by the alternate processes have the same purity profile as the principal process. A list of all relevant SOPs is recommended.

3.2. S.2.2.1 Schematic representation of the manufacturing process:

A complete visual representation of the manufacturing process flow should be provided for each immunogenic substance. For multiple active/immunogenic substances prepared from a single strain, a common flow chart is acceptable, through the propagation and harvest cycle, with indications of where the processing diverges. Further to that, steps in production, including incubation times and temperatures, equipment and materials used in each area where the operation is performed, and a list of the in-process control tests and end-product tests performed at each step should be clearly shown. In-process holding steps should be included with time and temperature limits indicated.

For chemical synthesis, a flow chart should include all the steps in a general synthesis cycle with other specific steps, such as fragment condensation or peptide cleavage, indicated. This diagram should also include information on the methods used to transfer the product between steps, (e.g., open transfers under laminar flow units). Such transfers should be described for movement of product between equipment, areas, rooms, buildings, and sites. Manufacturing steps which are computer controlled should be identified. Reference may be made to other sections of the application for more detailed process information. If equipment is dedicated to specific areas or products, it should be identified.

3.2. S.2.2.2 A narrative description of the manufacturing process:

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should describe each process step in the manufacturing process for each immunogenic substance starting from the Working Seed (WS) and Working Cell Bank (WCB)s. A list of all the components used in the manufacturing process including media, solvents or solutions should also be provided.

The narrative description should be provided for:

3.2. S.2.2.2.1 Propagation and Harvest

For each immunological substance/antigen production method or combination of methods, a growth curve or tabular representation of growth characteristics for each propagation step should be provided. A table showing yield, purity and viability (if applicable) of the crude harvest should also be included. A description of the assignment of batch numbers and how each batch of a stabilized intermediate containing multiple drug substances can be related to its component harvests and batches of individual drug substances should be included.

Propagation

This section should contain descriptions of:

- each step in the propagation from retrieval of the WCB to culture harvest (stages of growth)
- the media used at each step (including a statement on the quality of water used), with details of their preparation and sterilization
- the inoculation and growth of initial and sub-cultures, including volumes, time and temperature of incubation(s)
- how transfers are performed
- precautions taken to control contamination
- in-process testing which determines inoculation of the main culture system
- in-process testing to ensure freedom from adventitious agents, including tests on culture cells, if applicable
- 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)
- the parallel control cell cultures, if applicable, including number and volume of culture vessels
- induction of antigen, if applicable; and
- the use of antibiotics in the medium and rationale, if applicable.

Harvest

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

- the process parameters monitored
- the criteria for harvesting
- the determination of yields; and
- the criteria for pooling more than one harvest, if applicable.
- A 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.

This section should include a working definition of a harvest "batch." A description should be provided of the precautions taken to maintain aseptic conditions and prevent contamination during harvesting.

3.2. S.2.2.2.2 Purification and Downstream Processing

A description of the methods and materials used to separate and concentrate the intermediate forms and the final bulk of the immunogenic substance from the cells, media, solvents or solutions used in the production process should be provided. This description of each step of the purification process should also include the accompanying analytical tests developed or adopted by the manufacturer to show identity, purity, and concentration, and the levels of product related and other impurities that are process related etc. This is particularly important if the latter materials are determined to be toxins, carcinogens, teratogens, or allergens. Antibiotics and other components (e.g., growth factors, antibodies) used in the culture but neither required nor specifically intended to be in the final vaccine product should be removed before use. Procedures to assure containment and prevention of contamination or cross contamination should be provided.

i. 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 on:

- how culture purity is verified before inactivation, including the pre-inactivation titres.
- the method(s) and agent(s) used for inactivation.
- the method(s) undertaken to prevent aggregation and assure homogeneous access of inactivating agent(s) to the culture.
- the stage in production where inactivation or killing is performed
- the parameters which are monitored.

Verification of the adequacy of and margin of safety achieved by the method of inactivation or killing should be provided

ii. Purification (if appropriate)

A description of any methods used, including the objectives and rationale, for purification of immunogenic substance / antigen from crude harvest should be provided. This should also include:

- specialised equipment such as columns
- ultracentrifugation, ultrafiltration, and custom reagents such as monoclonal antibodies
- the process parameters (list of in-process controls) monitored
- the determination of yields, purity and biological activity
- in-process testing (e.g., sensitivity and specificity of ELISA)
- the criteria for pooling more than one batch, if applicable
- sterility or bioburden monitoring and the precautions taken to prevent contamination during purification
- the reuse and/or regeneration of columns and adsorbents; and

- monitoring, 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 (residual impurities) and leachable agents.

The time points at which testing is performed should be included in both the Flow Chart and the Batch Records. A list of the final acceptance criteria for the purified active/immunogenic substance should also be provided. If the purified active/immunogenic substance is held prior to further processing, a description of the storage conditions and time limits should be included. Verification of the stability of the purified substance under the conditions described should be included.

iii. Stabilisation Process (if applicable)

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

A description of steps taken to control bioburden and precautions to prevent contamination during these processes should also be given. If the stabilized intermediate is held prior to further processing, a description of storage conditions and time limits should be included. Verification of the stability of the immunogenic substance under the conditions described should be provided.

iv. Detoxification (if appropriate)

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

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

v. *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.

Production and Quality control of Synthetic Peptide

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

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 semisynthetic conjugated molecule, derivatised molecule, or subunit, including intermediate forms of the reactants and immunogenic substance should be stated.
- 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.
- 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.

Specification

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

Genetic Constructs and Recombinant Cell Lines

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

Host Cells

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

Gene Construct

A detailed description of the gene which was introduced into the host cells, including both the cell type and origin of the source material, 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 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.

Vector

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

Final Gene Construct

A detailed description should be provided 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. A restriction enzyme digestion map indicating at least those sites used in construction of the final product construct should be provided.

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 extrachromosomal), 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.2.3 Control of Starting Materials

(including MCB & MS)

A list of all materials (including culture media, buffers, resins for peptide synthesis, chemicals) used in the manufacture of the immunogenic substance should be provided, identifying where each material is used in the process. Adequate specifications and the reference standard for each of these materials should be provided. The specifications should address the characteristics of the material and its suitability for the intended use. For purchased starting materials, representative CoAs from the suppliers or manufacturer should be provided to demonstrate quality of the raw materials used. Process gases (compressed air, carbon dioxide, nitrogen) and water are considered raw materials.

Other reagents, such as monoclonal antibodies, enzymes, other proteins, uncommon amino acids and derivatives, or glycolipids, used in purification or production of the immunogenic substance, should be described in detail. The description should have identification of the vendor/supplier, specificity, and origin, including the manufacturing scheme, if applicable.

3.2. S.2.3.1 Cell Seed

If a virus can be grown efficaciously on cell lines, no mammalian primary cells should be used.

3.2. S.2.3.1.1 Animal Sources (where applicable)

Detailed information on any animals used for the propagation of microorganisms, or production of recombinant proteins for use as vaccines should include, but not limited to:

- the species and age of the animals
- the health status of the animals, e.g., specific pathogen free
- the results of adventitious agent screening

- the animal husbandry practices, e.g., quarantine procedures, used to ensure the suitability of the animals
- the veterinary and laboratory monitoring used to ensure the suitability of the animals
- a description of the inoculation of the animals; and
- a description of the tissues harvested and the method of harvest.

3.2. S.2.3.1.2 Cellular Sources

Cell substrate refers to microbial cells or cells/cell lines of animal (insect or mammalian) origin. Cell seed lot systems are frequently adopted for cells or cell lines. Details of the cell seed lot system should be submitted as explained in section below. The history and general characteristics of the cell lines should be provided. All specific procedures used to generate the cell substrate should be well documented and submitted as outlined in the following sections. The growth pattern and morphological appearance of the cell lines, from the master cell bank to the end-of production cells, should be submitted. A thorough discussion of the adventitious agent profile of any cell substrate should be provided.

3.2. S.2.3.1.2.1 Animal Cells

Cells of animal origin may harbour adventitious agents and consequently pose a potentially greater risk to animals and /or humans if not properly controlled. The measures taken to remove, inactivate, or prevent contamination of the product from any adventitious agent present in the cell substrate should be described.

3.2. S.2.3.1.2.1.1 Primary Cells (where applicable)

For most mammalian vaccines, use of primary cells is not acceptable. Instead cell lines should be used. In cases where primary cells are used, a discussion of the rationale for their use should be provided. In these cases, the primary cells should be obtained from herd or flock free from the specified pathogens with complete protection from introduction of diseases (adventitious agents). In the case of chicken flocks, these should comply with the requirements of the European Pharmacopoeia monograph for SPF chickens. For all other animals and species of birds, the herd or flock must be shown to be free from appropriate pathogens. All the breeding stock in the herd of flock intended to be used to produce primary cells for vaccine manufacture must be subject to a suitable regime such as regular serological checks carried out at least twice a year and two supplementary serological examinations performed in 15% of the breeding stock in the herd between the two checks mentioned above.

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

highest passage of primary cells must be checked in accordance with Table 1 and the procedure and results should be provided

The information submitted for each primary cell line used should include, but not limited to:

- the species and age of the animals and the source tissue from which the cells are derived
- the health status of the animals from which the cells are derived, e.g., specific pathogen free
- the animal husbandry practices (quarantine, etc.) used to ensure the suitability of the animals
- the veterinary and laboratory monitoring used to ensure the suitability of the animals
- a description of the preparation of primary cell substrates; and
- an explanation of the concurrent testing done to demonstrate the absence of adventitious agents and the results of those tests.

Table1: QC control of Primary Cells

Test	MCS	WCS	Cells from WCS at Highest Passage level
General microscopy	+	+	+
Bacterial/Fungi sterility	+	+	-
Mycoplasma	+	+	-
Viruses absence	+	+	-
Identification of species	+	-	-
Retroviruses	+	+	-

3.2. S.2.3.1.2.1.2 Cell Lines

As alluded to earlier, cell lines should be managed according to a cell seed lot system. Cell lines may consist of a continuous cell line or diploid cell strain of human or animal origin.

For human cells, the source of cells, including the materials and methods used, the tissue or organ of origin, ethnic and geographical origin, age, gender and general physiological condition should be clearly described. The health or medical history of the donor, if known, should be provided along with the results of any tests for pathogenic agents.

For animal cell lines, relevant descriptions of the source may include species, strains, breeding conditions, tissue or organ of origin, geographical origin, age, gender, and general physiological condition of the original donor. Testing for detection of adventitious agents should be undertaken with consideration of the possible agents which may be present in the cells. Results of all testing should be included.

a. Cell Bank System

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

- history /origin of the cell seed

- the banking system used, and identification of the cell seed
- the size of the cell banks
- the container and closure system used
- a detailed description of the methods, reagents and media used for preparation of the cell banks
- the conditions employed for cryopreservation and storage
- in-process controls; and
- storage conditions.

A description should be provided of 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. A discussion of precautions taken to prevent any catastrophic event that could render the cell banks unusable and to ensure continuous production of vaccines, for example, storage of cell banks in multiple freezers or at different sites, should be included. The cell bank system generally, consists of two tiers: a Master Cell Bank (MCB), and a Working Cell Bank (WCB) generated from the MCB for vaccine manufacturing. In some instances, another tier of 'Primary Cell Bank' may be established which allows the manufacturers to perform extensive testing on a pool of cryopreserved primary cells prior to their usage in vaccine production.

Table2: QC control of Cell Lines

Test	MCS	WCS	Cells from WCS at Highest Passage level
General microscopy	+	+	+
Bacterial/Fungi sterility	+	+	-
Mycoplasma	+	+	-
Viruses absence	+	+	-
Retroviruses	+	-	+
Identification of species	+	-	+
Karyology	+	-	+
Tumorigenicity	+	-	-

i. Master Cell Bank

The cells comprising the MCB should be uniquely identified and a complete history and characterization of the MCB should be provided, including, as appropriate for the given cells:

- the biological or chemical method used to derive the cell bank
- biochemistry (cell surface markers, isoenzyme analysis, specific protein or mRNA, etc.)
- specific identifying characteristics (morphology, serotype, etc.)
- karyology and tumorigenicity
- virulence markers
- genetic markers

- purity of culture; and
- media and components (e.g., serum).

For recombinant products, the cell substrate used to establish the MCB is the transfected cell containing the desired genetic construct which has been cloned from a single cell progenitor. For non-recombinant products, the cell substrate is the cell from the parental cell line chosen for preparation of the MCB without further modification. For a diploid cell line, the population doubling level chosen for the MCB should be given. The MCB should be stored at -70˚C or lower.

ii. Working Cell Bank

This section should contain a description of the procedures used to derive a WCB from the MCB. The description should include the identification system used for the WCB as well as the procedures for storage and cataloguing of the WCB to ensure maximum number of passages permitted will not be exceeded. 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. Also, a description of the methods and procedures used to assure culture purity and identity should be provided.

WCB should not be more than 20 passages from MCB, otherwise data to demonstrate that production cell seed is essentially similar to the MCB, w.r.t biological characteristics, purity and that cells do not have deleterious effects on the vaccine should be provided.

Ref: Ph. Eur. Monographs 5.2.4 and 5.2.2 as read with Ph. Eur. Monographs 0062

3.2. S.2.3.2 Viral or Bacterial Seed Material

This section should contain a description of the species, strain and known genotypic and phenotypic characteristics of the microorganism from which the immunogenic substance is derived. Microbial cells and their derivatives used as the vaccine drug substance include whole cell vaccines (live or killed), crude lysate or purified immunogens, recombinant DNA products, conjugates, and plasmid DNA vaccines.

The history and characteristics of each strain used to produce the product and a complete strain description should be provided, including:

- origin of isolate
- species
- biochemistry (fermentation profile, etc.)
- strain identifier and specific identifying characteristics (serotype, etc.)
- virulence (attenuation method, if performed)
- genetic characterization, if known (markers, inserts, deletions, etc.)
- plasmids; and
- genetic stability.

In the case of the virus vaccines, a detailed description of the virus seed used for vaccine production should be provided. The information submitted should include, but not limited to:

- the original source of the virus
- the passage history of the virus strains
- details of the seed lot system
- the culture techniques for virus seed maintenance

3.2. S.2.3.2.1 Master Seed (MS)

3.2. S.2.3.2.1.1 Virus seed

Viruses used in the manufacture of vaccine should be handled in a Seed Lot System. A record of the origin, passage history (including purification and characterisation procedures) and storage conditions should be maintained for each Seed Lot. Each MSV should be assigned a specific code for identification purposes.

The MSV shall normally be stored in Aliquots at -70°C or lower if it is in liquid form or at -20°C or lower if in a lyophilised form. Production of vaccine should not normally be undertaken using virus more than 5 passages from the MSV. Where the MSV is contained within a permanently infected MCS, the following tests shall be carried out on an appropriate volume of virus from disrupted MCS. Where relevant tests have been carried out on disrupted cells to validate the suitability of the MCS, these tests need not be repeated.

Each Master Seed Virus (MSV) shall be tested in accordance with current Ph. Eur., Monograph 0062 as read with any other topic specific monograph. The following tests should be performed: identity, bacterial and fungi sterility, mycoplasma [VICH GL34], extraneous agents.

3.2. S.2.3.2.1.2 Bacterial seed

The bacteria used in the manufacture of a vaccine should be identified by genus and species (and varieties where appropriate) and should be handled in a Seed Lot System wherever possible. Each Seed Lot shall be assigned a specific code for identification purposes. A record of the origin, date of isolation and designation of the bacterial strains, the passage history including purification and characterisation procedures), storage conditions should be maintained for each master seed lot.

Each Master Seed Lot shall be tested in accordance with Ph. Eur., Monograph 0062 as read with any other topic specific monograph. The following tests should be performed: identity and purity

3.2. S.2.3.2.2 Working seed (WS)

Working seed shall be derived from one or more container of Master seed. The minimum and maximum number of subcultures of each Seed Lot prior to the production stage shall be specified. The methods used for the preparation of media / cultures, preparation of suspensions for seeding, techniques for inoculation of seeds, titre and concentration of inoculate and the media used shall be described. It shall be demonstrated that the characteristics of the seed material (e.g. dissociation or antigenicity) are not changed by these subcultures.

The conditions under which each working seed lot is stored shall be described. The Working Seed shall be characterized in the same way for the Master seed.

3.2. S.2.3.3 Other substance of Animal Origin

Use of substances of animal origin should be minimised as much as possible. All these substances e.g. serum, albumin, trypsin, if used in vaccine production should be prepared in such a way as to prevent contamination of the vaccine with any living organism or toxin. Species of origin and Country of origin of the species should be declared. These substances should be sterilised using validated methods. The following tests should be performed using validated test procedures: extraneous agents, bacterial/fungi sterility.

Ref: Ph. Eur., Monograph 5.2.4 as read with Ph. Eur., Monograph 2262 and 5.2.8 among other monographs/EU guidance documents

3.2. S.2.3.4 Minimising risk of TSE/BSE

Biological starting materials should be sufficiently controlled to ensure that they do not contaminate the final product with extraneous infectious organisms. In the case of BSE/TSE, efforts should be made to minimise risk by selecting starting materials of animal origin from BSE/TSE free animal populations or geographical origins etc.

Documentation (Letter of attestation and CEP) to demonstrate that the starting materials are TSE compliant should be submitted.

Ref: Ph. Eur., Monograph 5.2.8

3.2. S.2.3.5 Media Preparation

The composition, method of production, Sterilisation process, the quality controls applied to these media (especially with regards to extraneous agents) and storage of the media should be provided, where necessary. 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. Any substance of animal origin included in the media should be described. Information (manufacturer's specifications, CoAs) on the constituents of the media should be provided. If the information is deemed proprietary and confidential, the supplier of the information should provide the information directly to the Authority.

3.2. S.2.4 Controls of Critical Steps and Intermediates (In-process control tests)

The manufacturer should identify and control key/critical manufacturing steps that could impact the quality and performance of the IVMP. Tests and acceptance criteria performed at critical steps identified in the manufacturing process should be described and justified based on relevant experimental data in order to verify consistency of the manufacturing process.

A critical step is defined as one where the process conditions, test requirements or other relevant parameters must be controlled within predetermined limits to ensure that the product meets its specification. The specifications, and acceptance criteria should have been established during process development and or process validation. The critical in-process tests should be adequately validated. Examples of these in-process control tests include:

- Cell counts/ optical density/ virus titre
- pH
- purity
- inactivation or detoxification (tested as soon as possible after end of inactivation or detoxification process and after neutralisation, it this is the case, but before the next step of production). NB. Inactivation kinetics and validation of inactivation test
- residual inactivating agent (inactivant)
- sterility

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. S.2.5 Process Validation

Process Validation

A summary report, including protocols and results shall 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 shall demonstrate the variability in each process as it relates to final specifications and quality.

Control of Bioburden

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 shall be provided.

3.2. S.2.6 Manufacturing Process Development

The developmental history of the manufacturing process described in 3.2. S.2.2, should be provided. The description of change(s) made to the manufacturing process of immunogenic substance batches used in support of the marketing application (e.g., nonclinical or clinical studies) should include, for

example, any changes to the process or to critical equipment. The reason for any of the changes should be explained. Information on immunogenic substance batches manufactured during development, such as the batch number, manufacturing scale, and use (e.g., stability, nonclinical, reference material) in relation to the change, should be provided.

The significance of the change should be assessed by evaluating its potential to impact the quality of the immunogenic substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant immunogenic substance batches should be provided to determine the impact on quality of the immunogenic substance. A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s) and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross- reference to the location of these studies in other modules of the submission is considered acceptable.

3.2. S.3 Characterisation

3.2.S.3.1 Elucidation of Structure and other Characteristics

Refer to information provided in 3.2. S.1.2 and 3.2. S.1.3 above. Any additional characterisations tests performed, but not covered in the sections above should be included in this section.

3.2. S.3.2 Impurities

A discussion should be provided of the potential and actual impurities arising from the manufacture, or degradation of the immunogenic substance, particularly from chemical starting materials/reagents e.g., inactivating agents or preservatives, where necessary.

3.2. S.4 Control of the Immunogenic Substance (bulk Antigen)

3.2. S.4.1 Specifications

The IVMP manufacturer's immunogenic substance specifications should be provided. At release, the following tests should be performed as a minimum:

- identity test
- antigen content: Cell counts/ optical density/ virus titre
- pH
- purity
- inactivation or detoxification (tested as soon as possible after end of inactivation or detoxification process and after neutralisation, if this is the case, but before the next step of production). NB. Inactivation kinetics and validation of inactivation test
- residual inactivating agent (inactivant)
- sterility

Ref: VICH GL40

3.2. S.4.2 Test Procedures

Details of the analytical procedures used for testing the active immunogenic substance should be provided. They should be described in such a way that they can be repeated by an Official Biological Control Laboratory.

The version (e.g. code number/version/date) and the reference standard (e.g. Ph. Eur. or In-House) of the Analytical Procedure should be provided for version control purposes. For each test parameter, the analytical method used should be specified e.g. ELISA, PCR etc.
Ref: VICH GL40

3.2. S.4.3 Validation of Test Procedures

Validation data, in the form of validation protocols and reports, including experimental results for the test procedures used for the control of the active immunogenic substance, should be provided unless the methods are pharmacopoeial, and the manufacturer/applicant have demonstrated that the stated pharmacopoeial methods are suitable for controlling their active immunogenic substance quality. All non - pharmacopeial methods should be validated.

3.2. S.4.4 Batch to Batch Consistency

Provide at least three consecutive production batches of the active immunogenic substance 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. The manufacturing records of these three batches should also be provided.

3.2. S.4.5 Description of batch identification system

A batch identification system for the lots at the various production stages e.g., filling, lyophilization (if it applies) and packaging should be provided.

3.2. S.5 Reference Standards

Information on the reference standards or reference materials used for testing of the immunogenic substance should be provided. The source(s) of the reference standards or materials used in the testing of the active substance should be provided (e.g. those used for the identification, purity, potency/cell counts/virus titre tests). These could be classified as primary or secondary reference standards. A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. Ph. Eur.) where one exists, and the lot number should be provided.

In cases where there is no pharmacopoeial reference standard, the criteria for establishing the primary reference substances should be provided with full analytical profiles. This should include specifications, full analytical and physico- chemical characterizations, etc. as shown in section 3.2.S.3.

The procedure for establishing secondary reference standards or materials normally used for routine analysis should be stated. Certificate(s) of analysis of reference standard or materials used should also be provided.

3.2. S.6 Bulk Antigen Container Closure

A description of the container closure system (critical dimensions with drawings), details of materials of construction, specifications with suitable or specific test for identification (e.g. IR) and analytical procedures should be provided for each primary CCS component. The same should be submitted for the secondary CCS (where applicable). If the container closure system is critical for assuring the quality of the immunogenic substance, its suitability should be justified. Depending on nature of the immunogenic substance, aspects that may need justification include choice of the primary packaging materials, protection from light and/or moisture, compatibility with the immunogenic substance including sorption to material and leaching and/or any safety aspects of materials of construct. Evidence of container closure integrity should be provided for the duration of the proposed shelf-life. If novel containers have been proposed, 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.

Reference to stability data can be additional supportive information to justify suitability of the proposed container closure system. The information should cover the whole packaging including the primary packaging material and secondary packaging (if applicable).

3.2. S.7 Stability

Ref: VICH GL17

Evidence should be provided to demonstrate that the bulk antigen is stable for the proposed period of storage, prior to final IVMP formulation or any intermediate/in-process material at each holding step.

3.2. S.7.1 Stability Protocol, Summary and Conclusions

Where the bulk antigen is to be stored after manufacture but prior to formulation into the final product, 6 months Accelerated (25°C ± 2°C/60% RH ± 5% RH) and 12 month Long-term (5°C ± 3°C) stability data should be provided for at least three consecutive batches, for which manufacture, and storage are representative of the commercial production scale. The bulk antigen should be stored in the intended bulk antigen/ in-process material CCS at all the storage conditions (temperature, humidity, light), where necessary.

Bulk Antigen intended for storage in a freezer, only 12 months real time (-20°C ± 5°C) stability data should be provided. In this case, due to absence of accelerated stability data, testing on a single batch at an elevated temperature (e.g., 5°C ± 3°C or 25°C ± 2°C) for an appropriate time period should be conducted to address the effect of short-term excursions outside the proposed label storage condition, e.g., during shipping or handling. Drug substances intended for storage below -20°C should be treated on a case-by-case basis.

N.B. The storage temperature should be stated and the results of stability tests on the batches should be provided. Below are examples of stability indicating tests that should be performed:

- Sterility at time 0 and end of storage period

- Potency/virus titre/bacterial count
- Physical and chemical test, as may be considered appropriate, e.g.,
  - Quantitative assay of preservatives.
  - pH of liquids/Osmolality

3.2. S.7.2 Stability Data

The data should reflect the batch numbers of the batches studied and the time points of testing. A minimum of six months stability data at the time of submission should be submitted in cases where storage periods greater than six months are requested. For drug substances with storage periods of less than six months, the minimum amount of stability data in the initial submission should be determined on a case-by-case basis.

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

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

3.2. P: IMMUNOLOGICAL VETERINARY MEDICINAL PRODUCT

3.2. P.1 Description and Composition of the IVMP

The IVMP submission should include the following:

3.2. P.1.1 Description of the dosage form

A description of the IVMP intended for marketing in Botswana should include the dose, appearance, type of container closure system, proposed storage conditions, and shelf-life. Where applicable, the description should also include the accompanying reconstitution diluent and its container closure system and the recommended administration devices, where applicable.

3.2. P.1.2 Qualitative and Quantitative Composition (per Unit dose)

A table reflecting all components, including common names and grades, used in the manufacture of the of the IVMP and the diluents, the amount of each component per unit (e.g. cfu/titre units), the function of each component(e.g. antigen, solvent, adjuvants, other excipients including antimicrobial preservative, stabilisers, emulsifiers colourants etc.), the reference standard for each (e.g. Ph. Eur.) and a justification for any overages should be provided.

Component and quality standard (and grade, if applicable)	**Reference Standard**	***Name of the IVMP (including strength/dose and dosage form)***	
		Function	**Quantity per unit (mg)**
Active (immunogenic) ingredients			
Inactive ingredients (adjuvant/excipients/preservative)			

3.2. P.2 IVMP Development

Information on all the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes, and usage instructions of the IVMP are appropriate for the purpose should be provided in this section of the submission. These studies described here are distinguished from routine control tests conducted according to the specifications. IVMP manufacturer should identify and describe all the formulation and process attributes (critical parameters) that can influence batch reproducibility, IVMP performance and quality. Supportive data and results from specific studies or published literature can be included.

At a minimum, IVMP Development information should include:

- the quality target product profile (QTPP) as it relates to quality, safety, and efficacy, considering for example the route of administration, dosage form, immunogenicity, dose, and stability
- identification of potential critical quality attributes (CQAs) of the IVMP, so as to adequately control the product characteristics that could have an impact on quality
- a discussion of the potential CQAs of the immunogenic substance(s), excipients and container closure system(s) including the selection of the type, grade, and amount to deliver an IVMP of the desired quality

- rationale for the choice of the immunogenic substance(s) and relevance of the strain to local context (where MA is being applied)
- rationale of the manufacturing method, overages (volume and /or potency/titre), tests conducted and sterilisation as well as antimicrobial preservatives efficacy, where applicable.
- stability, including in-use stability

These features should be discussed as part of the product development using the principles of risk management over the entire lifecycle of the product

3.2. P.2.1 Components of the IVMP

3.2. P.2.1.1 Active (Immunogenic) Substance

The compatibility of the immunogenic substance with excipients listed in 3.2.P.1, and in the case of multicomponent IVMPs, the compatibility of active substances with each other w.r.t genetic recombination/reassortment and interference with individual immunogenicity profiles should be provided. In addition, key physicochemical characteristics (e.g., water content, pH, stability etc.) of the active immunogenic substance(s) that can influence the manufacturability, performance, and quality of the VMP should be discussed.

3.2. P.2.1.2 Excipients

The choice of excipients listed in 3.2.P.1, their concentration, and their characteristics that can influence the manufacturability, performance, and quality of the IVMP should be discussed, relative to their respective functions. Excipient – excipient/adjuvant compatibility should be discussed. Where novel excipients/adjuvants are used, full information on composition and function of the excipient/adjuvants in the formulation should be discussed. Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies. Antimicrobial preservatives are discussed in detail in section 3.2.P.2.5.

3.2. P.2.2 Finished Product (IVMP)

3.2. P.2.2.1 Formulation Development

The dosing regimen (vaccination schedule), route of administration, and proposed usage of the product and salient physico-chemical profile of the immunogenic substance (antigen) should be taken into consideration when designing the formulation of an IVMP. The rationale for the proposed formulation should be provided.

Liquid and Semi Solid Formulation:

The concentration of the key components (adjuvants, antimicrobial preservatives, antioxidants, emulsifiers, stabilisers etc.) in the formulation should be shown to be appropriate for their intended purpose by experimental data.

Antimicrobial preservatives should not be added to single dose preparations unless justified. Choice of preservative should be based on storage conditions, reconstitution, dilution before use and frequency of opening of the pack. Testing for efficacy of preservative should be done using properly validated methods, appropriate negative & negative controls, and suitable organisms. Syringeability should be demonstrated using the syringe and appropriate needles (usually those used in real practice). Large packs may require rigorous testing, including in-use shelf life studies. In- use shelf-life should be as short as possible for sterile parenteral or ophthalmic preparations, otherwise justification should be provided.

Antioxidants may degrade during manufacture or shelf-life of the product. Levels of the antioxidant should be justified and supported by suitable experimental data, to ensure sufficient activity is maintained throughout shelf-life and in-use period.

Compatibility with other products should be demonstrated especially for IVMPs. This includes physical and chemical compatibility with recommended diluents and materials of construct of administration apparatus for the recommended or anticipated period.

Aerosolised/Spray formulations:

Particle size/mass, delivery rate of droplets and delivered dose homogeneity are important parameters and studies to address these parameters should be provided.

Injection: IVMPs largely used as multidose preparations. Usually not based on aqueous, but frequently on oily or other non-aqueous media. Use and level of antimicrobial preservatives, or indeed the absence of microbial preservatives in these media must be justified. Injectable suspensions should be evaluated for their syringeability, sedimentation rates and ease of resuspendability. NB. Preservative only acceptable in a single dose vaccine vials/presentation if they are made from the same bulk intended for multi-dose presentations

Solid Dosage form:

Risk of chemical incompatibilities or instability is less significant in solids when compared to Liquids or semi solid preparations. Where a formulation is added to drinking water or milk replacer prior to administration, development studies should address particle size, ease and rate of dissolution and homogeneity if applicable. Stability over duration of use of the IVMP should be addressed. Due to microbiological consideration, in-use shelf life should not exceed 24 hours.

Thus, homogeneity of the formulation should be addressed at the development stage and confirmed during the validation of the manufacturing process.

3.2. P.2.2.2 Overages

Addition or inclusion of overages in the IVMP formulation of is generally discouraged unless justified. The justification for addition of overages may be to compensate for antigen loses during manufacturing and/or shelf-life. Unlike with pharmaceutical VMPs, Overages for the sole purpose of extending or compensating for API loses during shelf life may be acceptable, provided safety is demonstrated from well-designed clinical studies.

3.2. P.2.2.3 Physicochemical and Biological Properties

Parameters relevant to the performance of the IVMP, such as pH, dissolution, redispersion, particle size distribution, rheological properties, should be considered during pharmaceutical development studies. For Parenteral IVMPs, factors such as tonicity, globule size of emulsions, particles size/mass and shape, viscosity and/or syringeability should be addressed.

3.2. P.2.3 Manufacturing Process Development

The choice of a dosage form or delivery system, the manufacturing, filling, and packaging processes should be scientifically justified.

Process development studies should lay down the basis for process optimisation and validation requirements. The studies should address microbiological, physical, and chemical parameters and identify appropriate microbial/extraneous agent controls for the IVMP. Since terminal sterilisation is not possible due to heat lability of active immunogenic substances, aseptic processing should be considered unless justified.

In the event a different manufacturing process, from the process described in 3.2.P.3.3, was used to produce bio-batches (preclinical and Clinical) batches, a discussion should be provided together with comparative results of the IVMP batches from the two manufacturing processes.

3.2.P.2.4 Container Closure System

The suitability of the primary and secondary container closure system and accompanying devices, used for the storage and administration of the IVMP, including premixes and bulk VMP, should be adequately discussed and justified. The discussion should consider, e.g., choice of materials, compatibility of the materials of construction with the dosage form (w.r.t sorption to container and leaching), safety of materials of construction, protection of the IVMP from light and moisture, and performance (w.r.t fragmentation and self-sealability of the closure for multi-dose injectables, dose reproducibility where the CCS and/or device is used for administration of the IVMPs.

The justification should take into consideration the safety to the user and target animals, admixtures, or dilution where applicable, proposed method of manufacture. For instance, in the case of sterile products, the choice of CCS should take into consideration the need to allow optimum sterilisation of the IVMP. Appropriate studies should be performed to demonstrate integrity of the CCS, where necessary taking into consideration the need for child resistant packaging.

Sorption to container: Data should be provided to demonstrate that the manufacturer has considered the possibility of sorption of the components from the liquid and semi solid formulation (relevant to safety and stability) and possibly permeation through the container walls and administration sets.

Leaching: The manufacturer should provide data to demonstrate that there is no significant leaching into the liquid or solid powder preparations over the shelf-life of the IVMP. In the case where leachable products are noted, toxicology data should be provided to show consideration of the safety to target animal species.

Dose reproducibility: In cases where CCS and/or dosing device are used for administration of the IVMPs, evidence should be provided that a reproducible, and accurate dose of the IVMP is delivered under testing conditions. This should take into account the range of the proposed dosing regimen, the need to have homogenous resuspendability of suspensions prior to administration, where applicable.

Fragmentation and /or self sealability: For all multidose vials where the same vials could be used for a wide range of animals/species, the number of doses per vial may vary greatly. Thus, data should be provided to demonstrate the integrity of the closure is maintained even following the maximum number of potential IVMP withdrawals per vial. Refer to the Ph. Eur. Fragmentation and self-sealing tests and consider suitably adapting the test in relation to the number of punctures per vial and the needle gauge to simulate in-use conditions.

3.2.P.2.5 Microbiological Attributes

The microbiological attributes of the dosage form should be discussed. Also, the rationale for not performing microbial limits testing for any formulation, and the choice, amount and effectiveness of the antimicrobial preservative added in the any formulation should be provided. Acceptable justification of the amount of antimicrobial preservative added in the formulation would be the analyses results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. Ph. Eur. general chapters on antimicrobial preservatives) using a batch of the IVMP. If the lower bound for the proposed acceptance criteria for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the IVMP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria. A single primary stability batch of the IVMP should be

tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

For sterile products, the integrity of the CCS in relation to prevention of microbial contamination should be addressed.

3.2.P.2.6 Compatibility

The compatibility of the IVMP with reconstitution diluent(s) or dosage devices (e.g., precipitation of active immunogenic substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling. Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples. Where the labelling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, subvisible particulate matter and extractables from the packaging components) should be demonstrated in glass, PVC and polyolefin containers.

However, if one or more containers are identified in the labelling, compatibility of admixtures needs to be demonstrated only in the specified containers. Studies should cover the duration of storage reported in the labelling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labelling specifies co-administration with other VMPs, compatibility/interference should be demonstrated with respect to the principal IVMP as well as the co-administered VMP (i.e. in addition to other afore-mentioned parameters for the mixture, the assay and degradation levels of each co-administered VMP should be reported). Also, for multi-component live vaccines, genetic recombination and re-assortment should be studied.

3.2. P.3 Manufacture

3.2. P.3.1 Manufacturer(s)

The name, address, and responsibility of each of the facilities involved in the manufacturing, packaging, labelling, and testing of the IVMP should be provided. Blending of the bulk antigens with the excipient(s) is the first step in the IVMP manufacturing process.

The list of manufacturers should specify the actual physical addresses of the manufacturing site(s) involved, including block(s) and units(s), rather than the administrative offices. Telephone number(s), fax number(s) and email address (es) should be provided.

A valid manufacturing authorization / licence and Certificate of Pharmaceutical Product (CoPP) issued by the competent authority in the country of manufacture of the IVMP should be provided to demonstrate that the IVMP is manufactured and registered for use in the country of origin. IVMPs

should be registered in accordance with national requirements in the country of origin or country of manufacture. In cases where an IVMP is not registered in the country of origin, justification should be provided for the application to register such a product in Botswana.
For each site where the major production step(s) are carried out, a valid WHO-type certificate of GMP compliance or evidence of inspection by regulatory authorities from VICH/ICH or ICH associated countries, regulatory authorities that participate in the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme (PIC/s) or those regional NRAs recognised by the Authority (ref. recognition policy) should be provided.

3.2. P.3.2 Batch Formula

A table reflecting all active and non-active components, including common names and grades, used in the manufacture of the dosage form, the amount of each component per unit (e.g. cfu/titre) and per batch (e.g. kg/L for each proposed batch size), including the overages if any, the function of each component(e.g. adjuvant, emulsifier, stabiliser antimicrobial preservative etc.), the reference standard for each (e.g. Ph. Eur., In-House) and percentage composition should be provided, where applicable.

The following table provides an example of how to summarize unit and batch formulae as it relates to product development.

Component and quality standard (and grade, if applicable)	**Reference Standard**	***Name of the IVMP (including strength/dose and dosage form)***											
		Function	**Quantity per unit (mg)**	**%**	**Quantity per non-clinical batch (kg/l)**	**%**	**Quantity per clinical batch (kg/l)**	**%**	**Quantity per validation / stability batch (kg/l)**	**%**	**Quantity per production batch (kg/l)**	**%**
Active (immunogenic) ingredients													
Inactive ingredients (adjuvant/excipients/preservative)													

Component and quality standard (and grade, if applicable)	**Reference Standard**	***Name of the IVMP (including strength/dose and dosage form)***											
		Function	**Quantity per unit (mg)**	**%**	**Quantity per non-clinical batch (kg/l)**	**%**	**Quantity per clinical batch (kg/l)**	**%**	**Quantity per validation / stability batch (kg/l)**	**%**	**Quantity per production batch (kg/l)**	**%**

N.B. sizes and use of each batch should be declared.

3.2. P.3.3 Description of Manufacturing Process and Process Controls

As alluded earlier, blending of the bulk antigens with the excipient(s) is the first step in the IVMP manufacturing process. A flow diagram showing each step of the manufacturing process where materials enter the process, and critical steps where samples are taken for in-process control, intermediates tests and final IVMP controls should be provided. In addition, a narrative description of the key steps in the manufacturing process, including the sterilisation operations, aseptic processing procedures, filling, lyophilization (if applicable), and packaging as well as labelling and the scale of production should be provided. This should include the amount of ingredient added at each step, the equipment type and capacity, process parameters such as mixing times and speeds, processing temperatures or pH, and any precautions necessary to ensure product quality, such as control of humidity, temperature or pH, light, and maximum hold times for IVMPs, where necessary. Associated numeric values can be presented as an expected range. Generally, the maximum hold times for sterile VMPs is 24hrs.

Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either be referenced or filed in this section (3.P.2.3.3). For the manufacture of sterile products, the class (e.g. A, B, C etc.) of the areas should be stated for each activity (e.g. compounding, filling, sealing etc), as well as the sterilization parameters for equipment, container/closure, sterilization process etc.

The information above should be summarized in the QOS template and should reflect the production of the proposed commercial batches.

3.2. P.3.4 Control of Critical Steps and Intermediates

The manufacturer should identify and control key/critical manufacturing steps that could impact the quality and performance of the IVMP. Tests and acceptance criteria performed at critical steps identified in the manufacturing process should be described and justified based on relevant

experimental data in order to verify consistency of the manufacturing process. The test 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.3.5 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 Bioburden

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.4 Control of Excipients

This section will include information of other materials used in the manufacture of the FPP formulation, not included/covered in sections 3.2. S.2.3. These include components such as adjuvants, emulsifier, stabiliser antimicrobial preservative etc., usually materials of nonbiological origin. If for any given excipient (component), information has been provided in sections 3.2. S.2.3, cross referencing is considered acceptable.

3.2. P.4.1 Specifications

The specifications from the applicant or the VMP manufacturer should be provided for all excipients, including those that may not be added to every batch (e.g. acid and alkali), those that do not appear in the final IVMP (e.g. solvents) and any others used in the manufacturing process (e.g. nitrogen, silicon for stoppers).

If the standard claimed for an excipient is an officially recognized compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard, rather than reproducing the specifications found in the officially recognized compendial monograph. A copy of the monograph used should be provided.

If the standard claimed for an excipient is a non-compendial standard (e.g. In-House standard) or includes tests that are supplementary to those appearing in the officially recognized compendial monograph, a copy of the specification for the excipient should be provided.

For excipients of natural origin, microbial limit testing should be included in the specifications. Skip testing is acceptable if justified (submission of acceptable results of five production batches).

For oils of plant origin (e.g. soybean oil, peanut oil) the absence of aflatoxins or biocides should be demonstrated. The colours permitted for use are limited to those listed in the "Japanese pharmaceutical excipients", the EU "List of permitted food colours", and the USFDA "Inactive ingredient guide". For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the VMP manufacturer's specifications for the product including identification testing.

Ref: VICH GL39

As read with ICH Q6A, Handbook of Pharmaceutical excipients, and EC Directive 94/36/EC

3.2. P.4.2 Analytical Procedures and Validation

The analytical procedures used for testing the excipients should be provided. Copies of analytical procedures from officially recognized compendial monographs used should be submitted. Provide certificate of analysis of one batch of each excipient.

3.2. P.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Copies of analytical validation information are generally not submitted for the testing of excipients, except for the validation of inhouse methods where appropriate.

Ref: VICH GL1 and VICH GL2

3.2. P.4.4 Justification of Specifications

Justification for the proposed excipient specifications should be provided, where appropriate. A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided

3.2. P.4.5 Excipients of Animal Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data). For these excipients from animal origin, evidence or proof confirming that the excipients used to manufacture the VMP are without risk of transmitting agents of animal spongiform encephalopathies. Materials of animal origin should be avoided, whenever possible. A complete copy of the CEP (including any annexes) demonstrating TSE compliance should be provided.

Ref: ICH Q5A, Q5D, Q6B.

3.2. P.4.6 Novel Excipients

For excipient(s) used for the first time in an IVMP or by a new route of administration, full details of manufacture, characterisation, and controls, with cross references to supporting safety data should be provided according to the active substance and/or IVMP format.

3.2. P.5 Control of IVMP (Finished Pharmaceutical Product)

3.2. P.5.1 Specifications

The proposed release and shelf life specifications for the IVMP should be provided. Copies of the IVMP release and shelf-life specifications, which should be version controlled, signed, and dated by the responsible QA or designate. Specifications establish the criteria to which an IVMP should conform to be considered acceptable for its intended use.

The following tests should be included:

1. Appearance
2. Identity
3. Purity/Sterility
4. Safety in Target animal species
5. Potency/Titre
6. Other physico-chemical tests such as pH and, if applicable, adjuvant, Assay for preservative, residual humidity, viscosity, emulsion, residual inactivant, etc.
7. Impurities/degradation products

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified.

3.2. P.5.2 Analytical Procedures

Details of the analytical procedures used for testing the IVMP should be provided. They should be described in such a way that they can be repeated by an Official IVMP Control Laboratory. The version (e.g. code number/version/date) and the reference standard (e.g. BP or inhouse) of the Analytical Procedures should be provided for version control purposes. For each test parameter, the analytical method used should be specified (e.g. ELISA, PCR etc.). If a method is described in a monograph from an officially recognised international pharmacopoeia, reference is made to that pharmacopoeia. Any modified compendial or in-house analytical procedures should be adequately described, and justification be provided.

3.2. P.5.3 Validation of Analytical Procedures

Analytical validation data, in the form of validation protocols and reports, including experimental results for the test procedures used for the control of the IVMP, should be provided unless the methods are Pharmacopoeial, and the manufacturer/applicant have demonstrated that the stated Pharmacopoeial methods are suitable for controlling their IVMP Quality (verification).

The key test procedures used for determination of the identification, potency/titre, purity/sterility, and extraneous agents should either be validated if in-house or verified if compendial. For officially recognized compendial VMP assay methods, verification should include a demonstration of specificity, sensitivity, and repeatability (method precision). If an officially recognized compendial method is used

to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

It is the responsibility of the manufacturer/applicant to ensure that control of the VMP is performed in accordance with updated technologies, in the event of very old monographs.

3.2. P.5.4 Batch Analysis

A description of batches and results of batch analyses should be provided for at least three consecutive production batches. Results from the three consecutive batches should be provided in tabular form for ease of comparison. The descriptions should include the batch number, batch size, date of manufacture and place of manufacture (data from all manufacturing sites must be provided), results of tests performed, and uses of the batches. It should be declared whether the IVMP batches in question were used for preclinical and clinical studies (if relevant), stability, pilot, scaleup, or if available, commercial scale.

Copies of the certificates of analysis for these batches should be provided in the dossier and the company responsible for generating the testing results should be clearly identified.

Analytical results should be discussed, and the discussion should focus on observations noted for the various tests, rather than reporting comments such as "all tests meet specifications". For quantitative tests (e.g. individual and total impurity tests and assay tests), results should be expressed numerically. Results which only state that the material "complies", "within limits" or "conforms" with the test are considered insufficient.

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

3.2. P.5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in "3.2. S.3.2 Impurities". A discussion should be provided for all impurities that are potential degradation products (including those impurities identified in 3.2. S.3.2) resulting from interaction of the excipients or the container closure system and process related impurities.

3.2. P.5.6 Justification of Specifications

The proposed IVMP specification(s) should be justified. The justification/discussion should include rationale for the inclusion or exclusion of tests, evolution of tests, choice of methods and acceptance criteria, and any differences from the officially recognized compendial standard tests (where officially recognized compendial methods have been modified or replaced), test methods, or acceptance criteria.

In cases where justification for certain tests, analytical procedures and acceptance criteria have been discussed in other sections of the dossier, the applicant may just cross-reference to the respective sections of the dossier where the information is located.

3.2. P.5.7 Batch Identification System

If different from the identification system described in section 3.2. S.4.5, an appropriate batch identification system for the lots at the various production stages e.g., filling, lyophilization (if it applies) and packaging should be provided. Otherwise, the applicant may cross-reference to section 3.2. S.4.5.

3.2. P.6 Reference Standards or Materials

If the same reference standards used for testing the Immunogenic substance/antigens are used for testing the VMP, reference could be made to the section 3.2. S.5. Otherwise, information on the reference standards or reference materials used for testing of the final IVMP formulation should be provided. See Section 3.2. S.5 for information that should be provided on reference standards.

3.2. P.7 Container Closure

A description of the container closure system (critical dimensions with drawings), details of materials of construction, specifications including description and a suitable / specific test for identification (e.g. IR) and analytical procedures should be provided for each primary CCS component. The same should be submitted for the drug delivery devices for multidose solutions, emulsions, and suspensions, including protective barriers that help ensure stability or sterility and secondary CCS (where applicable). If the container closure system is critical for assuring the quality of the active substance, its suitability should be justified. Depending on nature of the IVMP, aspects that may need justification include choice of the primary packaging materials, protection from light and/or moisture, compatibility with the components of the IVMP including sorption to material and leaching and/or any safety aspects of materials of construct, and contamination. Primary packaging components are those that are in direct contact with the IVMP. These include container, closure, liner, desiccant, and the filler.

Information to establish the suitability (e.g. qualification) of the container closure system should be discussed in Section 3.2.P.2 and could also be inferred from stability data.

3.2. P.8 Stability

Ref: VICH GL17

Evidence should be provided to demonstrate that the product is stable for the proposed shelf-life of the IVMP formulation under the proposed conditions of storage. The ultimate proposed shelf life should be stated.

3.2. P.8.1 Stability Summary and Conclusions

Stability 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), provided this mimic 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 and the results of stability tests on the batches should be provided. A plan for on-going stability studies should be provided indicating the batch numbers of the batches under study and the time points when testing is planned.

Below are examples of stability indicating tests that should be performed:

- Sterility at time 0 and end of shelf-life
- Potency/virus titre/bacterial count
- Physical and chemical test, as may be considered appropriate, e.g.,
  - Moisture content in lyophilised vaccines (VICH GL26)
  - Test to quantify adjuvant
  - Viscosity in cases of oil adjuvanted vaccines
  - Quantitative assay of preservatives. In the case of multidose presentations, preservative efficacy should also be studied at the minimum and maximum time points as defined in Ph. Eur. Monograph 5.1.3 and at the lower preservative limit in the end of shelf life specification if there is a range. NB. Preservative only acceptable in a single dose vaccine vials/presentation if they are made from the same bulk intended for multi-dose presentations
  - pH of liquid vaccines and diluents

Target animal safety testing: for conventional vaccines it may be acceptable to omit the target animal safety test at each shelf life testing point. A short shelf life will be granted, if necessary, while evidence of stability is collected. 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.8.2 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.8.2.1 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.8.2.2 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.8.2.3 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 should be consulted. 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.

3.2. R: REGIONAL INFORMATION

3.2. R.1 Batch Production Documents

3.2. R.1.1 Blank Master Production Document (BMR & BPR)

The blank manufacturing documents indicating the proposed strength, commercial batch size, and manufacturing site should be provided. The details contained in the BMR should include, but not be limited to, the following items:

- Dispensing, processing, and packaging sections, reflecting all the relevant materials and operational details
- Identification of all equipment by type and working capacity
- Process parameters (e.g., mixing time, mixing speed, processing temperature range, etc.)
- List of in-process tests (e.g., appearance, pH, potency, purity etc.)
- Sampling plan and list of all the steps where sampling should be done (e.g. purification, ultrafiltration etc.)
- The number of samples that should be tested and the frequency of testing
- All the precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times, etc.)
- Theoretical and actual yields; and statements of compliance with the GMP requirements

3.2. R.1.2 Executed Production Document (BMR & BPR)

A list of batches (number, sizes and use e.g. validation, Biobatch, commercial or production scale) for which the executed production documents have been provided, should be provided in this section.

3.2. R.2 Regulatory situation in other countries

The registration status of the IVMP in all other countries where the application for MA has been submitted should be provided. This should include both favourable and unfavourable regulatory decisions, for example where the product marketing authorization was granted, withdrawn, rejected, deferred, or cancelled.

Module 4: SAFETY

4.1 Table of contents for the module

4.2.0 Introduction

Safety of immunological VMPs is of paramount importance and the following aspects needs to be considered,

- Safety to the animal receiving the IVMP, and any other animals in contact with treated animals
- Safety to the user, owner, and any other person in contact with the animal
- Safety to the consumer
- Safety of the environment

The following reference materials may be used to guide conduct of safety studies, compiling or assessment of safety data:

1. Ph. Eur. Monograph 5.2.6 or any of the specific disease monographs.
2. VICH GL44 and VICH GL41
3. Some of the EU guidelines:
    a. EMA/CVMP/315887/2017: use of adjuvanted veterinary vaccines
    b. EMA/CVMP/IWP/54533/2006: user safety to IVMPs, among other international guidance documents

General considerations when conducting safety studies are:

a. Safety should be assessed/studied in each of the target species.
b. Animals must be free of Abs against the test vaccine antigen (virus, bacteria, toxin etc). NB. Animals with low levels of Abs may be used if the animals have not been vaccinated before. In which case, base level Abs will be determined. However, for Poultry only use SPF chickens.
c. Safety should be assessed/studied for each recommended route of administration
d. The worst-case scenario should be considered during safety study performance, that is:
    i. Use most susceptible group of animals, from the target species (minimum age, seronegative or pregnant animals)
    ii. Use the batch containing maximum potency (for inactivated vaccines/immunosera), or maximum titre (for live vaccines). In the case of Live vaccines, this will be that batch with least attenuated passage. Generally, the MSV or MSV + 1.
e. Unless justified or specified by specific disease monograph, the number of animals used should comply with the Ph. Eur. Monograph 5.2.6, as follows:

i. Mammals: 8 animals,
ii. Fish: 50 fish per group. If fish vaccine is administered by immersion, bath the fish twice the recommended time, using a batch at twice the recommended vaccine concentration.
iii. Poultry: ≥3 weeks old: 8 birds per group and ≤3 weeks old: 10 birds per group

f. Animals should be monitored, daily for 14 days post administration (or post last dose administration in the case of repeated toxicity studies), observing and recording objective criteria such as rectal temperature, injection site reaction and effect on performance.
g. Unless justified or prescribed in specific monograph, the product complies with the test if no animal shows abnormal local or systemic reaction or signs of disease or dies from cause attributed to the IVMP and / or no adverse effect on progeny/offspring.

4.2.1 Laboratory Safety Studies

4.2.1.1 Single dose toxicity studies

The IVMP should be administered, at the recommended dose and for each recommended route of administration, to the most susceptible (youngest recommended age or pregnant) animals.

4.2.1.2 Overdose toxicity studies

The IVMP should be administered at the **10x dose** of live vaccine for each recommended route of administration (unless one route is shown to result in more severe effects) to the most susceptible (youngest recommended age, seronegative or pregnant) animals.

4.2.1.3 Repeated dose toxicity studies

The IVMP should be administered, at the recommended dose and for each recommended route of administration (unless one route is shown to result in more severe effects), to the most susceptible (youngest recommended age or pregnant) animals. The number of administrations must be not less than the maximum number recommended, and it should take into account the primary vaccination plus the first revaccination. Dose intervals should generally be at least 14 days, unless justified. This study can run concurrently with single dose study toxicity studies.

4.2.1.4 Reproductive performance studies

If the vaccine is recommended or may be used in pregnant animals or laying birds, the IVMP should be administered, at the recommended dose and for each recommended route of administration(unless one route is shown to result in more severe effects) in this category of animals. Where appropriate, reproductive performance of males and females, and any adverse effects on the progeny investigated. For pregnant animals, the IVMP should be tested in each of the specific periods of gestation recommended for use, e.g. using 24 animals for each of the 3 trimesters (≥8 animals per trimester) of pregnancy of cattle. If the IVMP booster dose is recommended, repeat dose after 14 days of initial dose. Ph. Eur. Monograph 5.2.6 states that pregnant animals should be monitored at

least daily until one (1) day post parturition. However, it is scientifically impossible to assess all the progeny effects and confirm viability of the progeny in just one day post parturition. Therefore, animals (including their progeny) should still be monitored for 14 days post parturition.

If not performed an exclusion statement should be included on the label unless a scientific justification of absence of risk is provided.

4.2.1.5 Residue studies

Where the IVMP is a live vaccine, and contains well-established zoonotic disease pathogens, a determination of residual vaccine microorganisms at the injection site may be required in addition to the dissemination studies.

4.2.1.6 Immunological toxicity studies

Where the IVMP is suspected to adversely affect the immune responses of the animals to which they are recommended and /or administered, or of its progeny e.g Live IBD virus, a challenge study should be performed. For example, administer IBDV, then vaccinate with NCDV then assess responses to NCD. The study should be designed to enable sound scientific conclusions.

4.2.1.7 Interaction studies

Studies should be undertaken to demonstrate lack of adverse effect on the safety of the IVMP when simultaneous administration is recommended or where administration of the IVMP is recommended as part of a vaccination schedule, with administrations within a short period of time e.g. puppies vaccines and poultry vaccines. Also, refer to EMA/CVMP/IWP594618/2010: requirements for combined vaccines and associations of IVMPs for further information.

4.2.1.8 Other special requirements for live vaccine studies

4.2.1.8.1 Spread of the vaccine strain:

spread of vaccine strain from vaccinated to unvaccinated target animals should be investigated using the recommended route of administration most likely to result in spread. Also, spread to non-target, but highly susceptible species to the vaccine strain should be demonstrated using literature data (review of published articles) is acceptable. Possible animal -to- animal passage numbers should be determined, including the possible effects.

4.2.1.8.2 Dissemination of the vaccine strain within the vaccinated animal:

Faeces, urine, milk, eggs, and oral, nasal or other secretions should be tested for presence of IVMP strain, where necessary, consider spread to predilection site for replication of the vaccine microorganisms. The study is performed using least attenuated passage (MSV or MSV +1). These studies and one for persistence at injections site are obligatory for vaccines containing well-established zoonotic disease pathogens and it helps determine withdrawal periods.

4.2.1.8.3 Reversion to / increase in vaccine strain virulence:

Unless otherwise prescribed in a specific monograph, the Ph. Eur. Monograph 5.2.6 (and guidance in the VICH GL 41) should be considered. The study is performed using least attenuated passage (MSV or MSV +1). No special requirement for susceptible animals. Animals at an age suitable for recovery of the strain. In-vitro propagation of strain is not acceptable. MSV should be administered using recommended route most likely to yield reversion to virulence and inoculum likely to contain maximum release titre. Four (4) serial passages in animals of target species are required. Two (2) animals per group or 5 birds should be used. During the last / final passage, a minimum of 8 animals and 10 birds per group should be used. This last / final passage should only be done if signs of reversion to virulence are noticed.

Signs of reversion to virulence include:

- *Difference in clinical sign profile between single dose toxicity study and the last / final passage, precisely increased clinical signs during the last / final passage.*
- *Increased strain titre in the last / final passage*

4.2.1.8.4 Biological properties of the vaccine strain:

Intrinsic properties of the vaccine strain e.g. neurotropism/stability of attenuation should be determined. In the case of vector vaccines, risk of changing tropism or virulence of the strain should be evaluated, including the specific tests to be carried out.

4.2.1.8.5 Recombination or genomic reassortment of the vaccine strain:

A discussion should be provided on probability of recombination or genomic reassortment with field or other strains. Literature review of published articles is acceptable.

4.2.2 Field Safety Studies

Field safety studies, investigates the safety of the IVMP under the different field conditions in different categories of the target species (e.g. different breeds, reproductive stage of male and female, pregnant populations etc.) and under different management practices. Studies should be performed in accordance with good clinical practices (VICH GL9). These studies should have due regard for animal welfare, the user, the consumer and the environment.

4.2.2.1 Target Animal Species Safety

IVMPs may present a range of potential risks of negative effects which may occur under the proposed conditions of use in animals. These potential risks should be evaluated in relation to the severity of the pathological condition concerned. A number of studies should be performed, and the results of the studies (range of which depending on formulation) provided

Ref: VICH GL 9, VICH GL41 and VICH GL44
As read with the Ph. Eur. Monograph 5.2.6 or any of the specific disease monographs

4.2.2.2 User Safety

Accidental exposure of the IVMP users has potential risk to cause problems to this population. As such, assessment of the risk presented from the IVMP for those handling and administering it, should be performed in accordance with the Guideline on user safety for immunological veterinary medicinal products EMA/CVMP/IWP/54533/2006 and it should be presented by incorporating the following aspects:

- an appraisal of the hazard of the IVMP:
- an appraisal of how and when the user will be exposed to the IVMP: consider,
  - the people administering the IVMP in view of vaccine containing well-established zoonotic disease pathogens
  - composition of IVMP e.g. mineral oil may cause necrosis to injected sites
  - administration methods e.g. vaccine aerosols may expose personnel to vaccine containing well-established zoonotic disease pathogens.
- conclusions of the above two aspects resulting in a risk characterization
- proposals of how the risks should be mitigated: e.g. PPC considerations.

It is important to clearly identify the users of the product and to include all users, some of which may not necessarily be administering the product but may be indirectly exposed to the product. A review of the published toxicity studies investigating local and systemic effects of the VMP is acceptable.

4.2.2.3 Risk assessment of veterinary drugs residues in food of animal origin: Consumer Safety

Exposure to IVMP residues can have several harmful effects to people, if the product was a live vaccine containing well-established zoonotic disease pathogens. Antibiotics should not be used as preservatives in vaccines. However, if used in the manufacture of the vaccine in the early production stages, study of residues will be required, unless MRLs are established. Non-active ingredients such as inactivating agents (formaldehyde, β-propiolactone (BPL), binary ethylenimine (BEI)), preservatives, adjuvants etc. should also be considered [VICH GL25]. Withdrawal periods should be decided based on results of the studies e.g. dissemination studies, residues studies and persistence at injection sites for live vaccine containing well-established zoonotic disease pathogens such as salmonella.

4.2.2.4 Environmental safety

IVMPs may also be considered a source of biological, organic and inorganic pollutants that leads to environmental safety and subsequently ecological safety concerns. Requirements for safety are important to avoid persistent damage to the environment. An assessment of the potential of exposure of the IVMPs to the environment shall be made taking into account:

(a) The target species

(b) Pattern of use (flock/herd) and the intrinsic properties of the pathogens (e.g. hot strains in live vaccines/stability and persistence of GMOs (live vector vaccines) in environment)

(c) The method of administration and whether it may lead to direct entry of the product into the environment, e.g. spray for chicken or water administration for fish vaccines

(d) Excretion of the IVMP
(e) The method of disposal of the unused, used products and containers

Studies on potential harmful effect of the product to the environment shall be provided. The environment shall include soil, water and air such studies shall include:
(a) Fate and behaviour in the soil
(b) Effects on soil organisms
(c) Fate and behaviour in water
(d) Effect on aquatic organisms
(e) Effects to other non-target organisms e.g. in the case of live vaccine containing well-established zoonotic disease pathogens such as salmonella.
Proposed measures to minimize the above potential risks during use of the product shall be described.
Ref: EMA/CVMP/IWP/074/95
As read with the Ph. Eur. Monograph 5.2.6 or any of the specific disease monographs

Module 5: EFFICACY

5.1 Table of contents for Module 5

5.2 Efficacy studies reports

During development, IVMPs are tested to demonstrate that they are efficacious when administered by each of the recommended routes and methods of administration, using the recommended schedule the target species, and the age group for which its use is to be recommended. The type and range of efficacy testing to be performed depends on the on the particulars of the IVMP. For instance, vaccines for:

i. ***Companion animals*** – like those for humans (Health and welfare of the individual are main targets. May need to consider the emotional attachment owners have with their pets, and zoonotic diseases)
ii. ***Livestock*** - limit impact of diseases on production parameters, cost benefit of vaccination may be considered
iii. ***Zoonotic / foodborne infections*** – reduce or eliminate risk for consumers, and improve productivity of the of individual animal
iv. ***Wildlife*** – zoonotic diseases, welfare concerns are of increasing importance

General considerations when conducting efficacy studies are:
- The dose to be used should be that quantity of the IVMP to be recommended for use
- The dose should contain the minimum titre or potency expected at the end of its period of validity
- For live vaccines, the product containing the virus / bacteria at the most attenuated passage level should be used

- For immunosera, the dose to be tested should contain minimum quantities of Immunoglobulin or gammaglobulin and /or total protein
- The efficacy evidence must support all claims being made for the IVMP.
- Claims of the onset and duration of immunity should be supported by data from trials.
- The influence of passively acquired or maternally derived Abs on the efficacy of an IVMP should be adequately investigated.
- Efficacy of each of the components of multivalent or combined vaccines should be demonstrated using the combined vaccine
- Studies of immunological compatibility should be undertaken when simultaneous administration is recommended and where the IVMP is part of a usual administration schedule
- When an IVMP is recommended as part of an administration scheme, the priming, booster effect or the contribution of the vaccine to the efficacy of the scheme should be demonstrated
- All results obtained, favourable or unfavourable, should be reported.

5.2.1 Challenge Studies:

Target animals should be challenged under the recommended conditions of use of the IVMP, under a well-controlled laboratory setting. The conditions should mimic, as much as possible, the natural conditions of infection, w.r.t. amount of challenge organism and route of administration of the challenge.

For vaccines: Unless justified, the challenge should be done using a strain different from the one used in the production of the vaccine. The immune mechanism responsible for the protection achieved by the vaccine should be determined, where possible.

For immunosera: Data should be provided from measurements of Abs levels achieved in the target species after administration of the IVMP as recommended. Where published data on protective Ab level exists, challenge studies may be exempted. The challenge may be given before or after administration of the IVMP, in accordance with the indications and specific claims to be made.

NB. Limitations: controlled conditions not reflective of real-life situation, may not mimic natural pathogen exposure, number of animals generally small and follow-up usually inadequate.

5.2.2 Laboratory trials

Several trials should be conducted. These include:

- ***Dose response study*** – needed to set the minimum efficacious dose level
- ***Onset of immunity study*** – the time interval between completion of the primary vaccination course and onset of the protective immunity should be determined.
- ***Duration of immunity study*** – *the time interval between completion of the primary vaccination course and the latest (last) time point where protective immunity was demonstrated. Usually this is just before the recommended time for the re-vaccination scheme, where applicable.*

- ***Efficacy of booster dose*** *– only applicable in cases where the IVMP is recommended for re-vaccination. Determined using a challenge study or serological parameters determination.*

5.3 Field Efficacy trials

Field trials (with untreated control animals) results should always be performed to supplement laboratory trials results, unless justified. They confirm results obtained from laboratory trials, under real-life conditions on a larger scale (sample size big enough to give the study enough statistical power), with different breeds, different husbandry systems and different production parameters. The studies should be conducted in accordance with GCP (VICH GL9)

Unless justified by animal welfare reasons, the field trials should always include untreated controls. Where laboratory trials cannot demonstrate or support efficacy, performance of only field trials is acceptable. Such cases include when there are:

- No suitable experimental infection model
- Multifactorial diseases (more than one pathogen)
- Special husbandry facilities involved (drinking water IVMPs) and when,
- Environmental factors play a major role in aetiology.

Safety and Efficacy can be investigated in the same study using a typical routine IVMP batch of intermediate titre or potency.

Ref: EMA/CVMP/IWP/206555/2010, EMA/CVMP/IWP/439467/2007, EMA/CVMP/682/99, EMA/CVMP/042/97 Rev.1, EMA/CVMP/852/99, EMA/CVMP/IWP/594618/2010 and EMA/CVMP/IWP/123243/2006 Rev.2
As read with the Ph. Eur. Monograph 5.2.6 or any of the specific disease monographs

ANNEX I: APPLICATION FORM

ANNEX II: QUALITY INFORMATION SUMMARY (QIS)

ANNEX III: QUALITY OVERALL SUMMARY (QOS)

ANNEX IV: IMMUNOLOGICAL VMPs SCREENING CHECKLIST