Botswana Medicines Regulatory Authority

Approved By: _____ **Mr Bathusi Kgosietsile Director-Product Evaluations and Registration**

_____ **Date of Approval (DD/MM//YY)**

Revision status sheet

Page	Changes made	Issue No	Process owner's name	Date
17	Grammar correction	2.0	Innocent Ravengai	17/08/2023
17	Inclusion of a statement on Prohibition of Use of Certain Active Substances	2.0	Innocent Ravengai	17/08/2023
1	Change in name of approving authority	1.0	Innocent Ravengai	05/10/2022
3	Update of the Table of contents	1.0	Innocent Ravengai	05/10/2022
16-26	Renumbering and rearrangement of Module 1	1.0	Innocent Ravengai	05/10/2022
22	1.2 Replaced CEP where available with API change control	1.0	Innocent Ravengai	05/10/2022
21-30	Added sections a, b, d, e, 1.31, 1.4, 1.5, 1.6 ,1.7, 1.8, 1.9 and 1.10	1.0	Innocent Ravengai	05/10/2022
21	1.3.1 Added 'and/ or Package Inserts'	1.0	Innocent Ravengai	05/10/2022
31-34	Deletion of Section 2.2 and placing it under 1.2	1.0	Innocent Ravengai	05/10/2022
46	Correction from negative & negative to Positive and negative	1.0	Innocent Ravengai	10/11/2022

Table of Contents

1. Purpose

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

2. Scope

This guideline applies to all pharmaceutical veterinary medicinal products registration applications containing APIs of synthetic or semi-synthetic origin. The guidelines cover both generic and innovator medicines.

3. Abbreviations and Definitions

3.1 Abbreviations

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

API	Active Pharmaceutical Ingredient
API MF	Active Pharmaceutical Ingredient Master File
BCS	Biopharmaceutical Classification System
BOMRA	Botswana Medicines Regulatory Authority
BP vet	British Pharmacopoeia – Veterinary Medicines
BTIF	Bioequivalence Trial Information Form
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
CTD	Common Technical Document
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
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
JP	Japanese Pharmacopoeia
MRSA	Medicines and Related Substances Act
NMRA	National Medicines Regulatory Authority PDF portable document format
Ph. Eur.	European Pharmacopoeia
PI	Package Insert
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation Scheme
PMF	Plasma Master File
QA	Quality Assurance
QIS	Quality Information Summary
QOS	Quality Overall Summary
SADC	Southern African Development Community
SPC	Summary of Product Characteristics (European)
TSE	Transmissible Spongiform Encephalopathy
USP	United States Pharmacopoeia
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
VMP	Veterinary medicinal product
VPP	Veterinary paraprofessional (as defined in the MRSA 2013)
WHO	World Health Organisation

3.2 Definitions

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

Active pharmaceutical ingredient (API) or drug substance - Any substance or mixture of substances used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of that pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body.

Active pharmaceutical ingredient (API) starting material- A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be commercially available, a material purchased from one or more suppliers under contract or commercial agreement or produced in-house (ICH Q7). See also starting materials for synthesis.

Applicant- A company/entity registered, licensed or operating in Botswana that submits 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.

Biopharmaceutics Classification System (BCS) highly soluble- An API for which the highest dose recommended by WHO (if the API appears on the WHO Model list of essential medicines) or highest dose strength available on the market as an oral solid dosage form (if the API does not appear on the WHO Model list of essential medicines) is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37˚C.

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

Reference product-A pharmaceutical product with which the new product is intended to be interchangeable in clinical practice. The reference product will normally be the innovator product for which efficacy, safety and quality have been established. Where the innovator product is not available, the applicant should consult the Medicines Regulatory Authority for suitable reference product.

Established generic (multisource) product- A multisource product that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years.

Existing API- An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority or by WHO but requires the filing of a dossier. This would include, for example, new VMP dossiers and variations to multisource products.

Finished pharmaceutical product (FPP) or drug product- A finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

Generic (multisource) pharmaceutical products- Generic pharmaceutical products are pharmaceutically equivalent or pharmaceutically alternative products that may or may not be therapeutically equivalent or bioequivalent. Generic products that are therapeutically equivalent are interchangeable.

Innovator pharmaceutical product- Generally, the innovator pharmaceutical product is that which was first authorised for marketing, on the basis of documentation of quality, safety and efficacy.

Manufacturer- A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pharmaceuticals.

Officially recognized pharmacopoeia-Those pharmacopoeias recognized in the WHO Prequalification of Medicines Programme (i.e. 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 API, or confirm or extend the shelf-life of the FPP.

Pilot-scale batch- A batch of an API or FPP manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For example, for solid oral dosage forms a pilot scale is generally, at a minimum, one-tenth that of a full production scale or 100 000 tablets or capsules, whichever is the larger unless otherwise adequately justified.

Primary batch- A batch of an API or FPP 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 API or FPP manufactured at production scale by using production equipment in a production facility as specified in the application.

Starting materials for synthesis- Materials that mark the beginning of the manufacturing process as described in an application or in an API master file (APIMF). A starting material for a synthetic API is a chemical compound of defined molecular structure that contributes to the structure of the API. See also API starting material.

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 opened for submission of applications for registration of Veterinary Medicinal Products with effect from 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 of VMP dossiers for submission to BOMRA. The Authority recommends the applicants to compile their VMP registration applications in CTD format. It also, provides recommendations on the quality information for the active pharmaceutical ingredients (APIs) and the finished pharmaceutical products (FPPs) that should be submitted to Botswana 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, for detailed guidance on submission of efficacy and safety data to support applications for registration of new (innovator) medicines.

Prohibition of Use of Certain Active Substances

BoMRA shall not register for use in **food-producing** animals, any formulation that contains active substances that are prohibited in accordance with;

1. Medicines and Related Substances (Prohibition of Use of Certain Medicines in Animals) Order, 2020 [S.I 76 of 2020]
2. Diseases of Animals Prohibition of Use of Anabolic Hormones and Thyrostatic Substances Regulations, 1987 [S.I 103 of 1987]
3. Directives from the Director of Veterinary Services in Botswana which seek to comply with European Union (EU) Commission, Commission Implementing Regulation (EU) 2022/1255 and any other EU regulations/ Directives.

It is recommended that prospective applicants refer to these pieces of legislation to ensure compliance of their formulations and labelling information.

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 – Quality (M4Q) as developed by ICH

4.1.3 Provide guidance on the technical and other general data requirements.

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

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 – Quality (M4Q) guideline, 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 guidelines described in other existing VICH or ICH and/or EMA's CVMP reference documents and guidelines. For those VMPs intended for use in food producing animals, applicants are encouraged to refer to the EU Commission Regulation 37/2010, Directives 96/22/EC and 96/23/EC as well as EC Regulation No 1831/2003 to ensure their active pharmaceutical ingredients are approved for use in food producing animals.

The quality of existing APIs and corresponding generic pharmaceutical VMPs should not be inferior to new APIs and reference VMPs. Therefore, the principles of the VICH, ICH and some EU guidelines

that are referenced throughout this guideline may also equally apply to existing APIs and generic products. 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 API or FPP. For instance, well known APIs would not require clinical studies and Oral solid dosage forms (FPP) do not require media fill studies. In such 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 submission of documentation (CDs) should be submitted in Microsoft Word (for required templates or summaries, e.g. QOS, QIS, BTIF) and text-selectable PDF format (for all other documentation) except for documents like executed BMRs, cGMP certificates, CoAs etc. 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 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 medicine, 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 the Botswana Guideline on submission of documentation for a finished pharmaceutical product (FPP): preparation of application 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).

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 FPP containing more than one API: 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 API from multiple manufacturers: one complete "3.2.S" section should be provided for the API from one manufacturer, followed by other complete "3.2.S" sections for each other API manufacturer.

d) for an FPP with multiple strengths (e.g. 10, 50, 100 mg): One complete application should be provided for each FPP strength.

e) 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.

f) for multiple FPPs (e.g. tablets and parenteral products): a separate dossier is required for each FPP.

g) for an FPP supplied with reconstitution diluent(s), one complete "3.2.P" section should be provided for the FPP, followed by the information on the diluent(s) in a separate part "3.2.P", as appropriate.

h) for a co-blistered FPP, one complete "3.2.P" section should be provided for each product.

For more information on when one or separate applications are required, applicants should refer Module 1.5.2 in the Botswana Guideline on preparation of applications in CTD format.

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.
- **Precursor:** a substance, including its salts, isomers, derivatives, and analogues, that may be used frequently in the illicit synthesis or manufacture of narcotic medicines, psychotropic medicines, and illicit substances as provided for under the United Nations Convention Against the Illicit Traffic in Narcotic Drugs and Psychotropic Substances, 1988
- **POM:** Prescription Only Medicine - a medicine, 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 medicine not containing narcotic or psychotropic substances which are dispensed by a pharmacist under prescription issued by a registered veterinary surgeon or veterinary paraprofessional (VPP) or by a registered veterinary surgeon or registered paraprofessionals in authorized premises. Supply of a prescription from veterinarian or a VPP is required.
- **General Sales Medicines:** a medicine 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.

1.0 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 substance
- 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.

1.1 Comprehensive table of Contents

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

1.2 Application Form

A completed signed and dated application form should be submitted for each VMP. All forms are to be completed in English. The application Form should be downloaded from the 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 medicine 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 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 declaration
d. CV of the qualified expert (s) for pharmacovigilance
e. API change control
f. Evidence of registration of the product in the country of Origin (CoPP or registration certificate)
g. Letter of access from the API MF holder or CEP holder,
h. QIS

a) Proof of payment of relevant application fees

Applicants should consult the current fee schedule for the correct and appropriate application fee for registration of veterinary medicines. A copy of the invoice or proof of payment of the application fees should be included in the application. 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.

b) Letter of authorisation for communication on behalf of the applicant

The suitably qualified person responsible for the compilation of the application must sign the application. This should be an original signature (scanned signature not acceptable). Attach an individualised, person specific letter of authorisation for the signatory, issued by the Person responsible for the overall management and control of the business (CEO).
A letter of Authorisation for the responsible person, if different from the person signing the dossier, to communicate with Botswana MRA should be submitted in this section.

c) 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.

d) Curriculum vitae of the qualified person responsible for pharmacovigilance

Include curriculum vitae of the qualified person responsible for pharmacovigilance.

e) API change control

A formal agreement exists between the manufacturer of the Finished Pharmaceutical Product (FPP) and each manufacturer of the active pharmaceutical ingredient (API), which ensures that information will be communicated between them and to the MRA before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except when permitted by the MRA's Amendments guideline relating to changes to medicines, such changes will not be made to the API(s) to be used in manufacture of medicines to be distributed in Botswana before written approval is granted by the MRA. Both parties understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines containing this material in Botswana.
A copy of the agreement between API and FPP manufactures should be submitted in this section.

f) Quality information summary (QIS)

The QIS template, ***BOMRA/ER/VET/P02/F03***, 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 API and FPP information from the assessment report (inter alia identification

of the manufacturer(s)/site addresses, API/FPP 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.

2.3. S. Active Substances

2.3. S.1 General Information

Information from 3.2.S.1 should be included

2.3. 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 API, 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

2.3. S.3 Characterisation of drug substance (name, manufacturer)

A summary of the interpretation of the evidence of structure, isomerism as described in 3.2.S.3.1 should be included. Data on potential and actual impurities arising from the synthesis, manufacture and /or degradation including the basis for and qualification of set acceptance criteria/limits for individual and total impurities should be included.

2.3. S.4 Control of Drug 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 API batch analysis data as provided in section 3.2.S.4.4 should be provided.

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

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

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

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

2.3. 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 summary of the post-approval stability protocol should also be included. A tabulated summary of the stability study results as provided in Section 3.2S.7.3 should be provided.

2.3. P. Veterinary Medicinal Products (name, dosage form)

2.3. 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

2.3. 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.

2.3. 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

2.3. 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

2.3. P.5 Control of Drug 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.

2.3. P.6 Reference Standards or Materials (name, dosage form)

A tabulated presentation of the information from 3.2.P.6 should be provided

2.3. P.7 Container Closure System (name, dosage form)

A brief description and discussion of the information, from 3.2.P.7 should be provided

2.3. 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

2.3. R. Regional Information

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

1.3 Product Labelling Information

1.3.1 SPC and/or Package inserts

Copies of the SPC or package insert, and information leaflets in accordance with recognised regional and / or international format e.g. https://www.ema.europa.eu/en/glossary/summary-product-characteristics 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).

1.3.2 Patient Information Leaflet

Patient information leaflet to be submitted where available.

1.3.3 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.

Product samples

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.

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

1.4 Information about the experts

Information to be provided where applicable.

1.5 Specific requirements for different types of applications

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

	Product type	**Required parts of the dossier**				
		Mod 1	Mod 2	Mod 3 (API & FPP)	Mod 4: Pre-Clin (Pharmaco-Toxicology)	Mod 5: Clinical (Safety & Efficacy)
1	Innovator	√	√	√	√	√
2	Innovator FDC	√	√	√	√	√
3	Innovator variants (strength, form, route of administration or Indication)	√	√	√	Bridging studies data	Bridging studies data
4	Generic (Single API/FDC)	√	√	√	X	*

Key

FDC: Fixed Dose Combination
API: Active Pharmaceutical Ingredient
FPP: Finished Pharmaceutical Product (VMP)
√: Required
X: Not required
* BE studies would be required for certain formulations. Refer to Module 5.

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

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

1.5.1.1 Different pack sizes for the same strength and formulation require one application
1.5.1.2 Different strength and / or formulation requires separate applications

1.5.2 Oral Liquids (Syrups/suspensions/solutions), Creams and Ointments
1.5.2.1 Different containers of the same strength and formulation will require one application
1.5.2.2 Same container size of different strength and/or formulation will require separate applications

1.5.3 Injectable Liquids and Powders (Ampoules, vials, Prefilled Syringes (PFS), Cartridges or large volume parenteral)
1.5.3.1 Ampoules containing parenteral preparations of different strength and formulation will require separate applications,
1.5.3.2 Ampoules containing identical parenteral preparations of the same strength and/or formulation, but different volumes will require separate applications,
1.5.3.3 Ampoules and/or single dose vials containing dry powder, crystals etc of different mass will require separate applications,
1.5.3.4 Dry powders or crystals etc. of the same respective mass, packaged in ampoules and single dose vials will require separate applications,
1.5.3.5 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,
1.5.3.6 Dental cartridges containing fluids of different volumes will require one application,
1.5.3.7 Ampoules containing "water for injection", but of different volume will require one application,
1.5.3.8 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,
1.5.3.9 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,
1.5.3.10 Multi-dose vials of the same strength and formulation in different volumes will require separate applications,
1.5.3.11 Multi-dose vials and a single dose ampoule of the same formulation will require separate applications,
1.5.3.12 Multi-dose vials containing dry powder of different mass and the same formulation, and having the same concentration when reconstituted will require one application,
1.5.3.13 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,
1.5.3.14 An ampoule of diluent to be used with any biological preparation will require one application,
1.5.3.15 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,
1.5.3.16 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,

1.5.3.17 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 preparations.

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

1.5.3.19 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.

1.5.4 Applicants/Proprietary names

1.5.4.1 Same formulation applied under different proprietary names will require separate applications Same formulation from different applicants will require separate applications

1.6 Environmental risk assessment

An application should be accompanied by an environmental risk assessment, evaluating any potential risks of the medicinal product to the environment.

The requirements relate to those risks to the environment arising from use, storage and disposal of medicinal products and not for risks arising from the synthesis or manufacture of medicinal products.

In case of extensive documentation for the environmental risk assessment should always be provided in a separate volume as part of Module 1. In case of a short statement, this can remain in the Module 1 volume(s).

1.7 Good Manufacturing Practices

For all medicines, irrespective of the country of origin, it is expected that all key manufacturing steps of the active pharmaceutical ingredients and finished pharmaceutical products 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:

1.7.1 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.

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

1.7.3 Manufacturing and Marketing Authorizations (Other international registrations obtained)

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

a) submitted and pending registration,
b) granted a marketing authorisation (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.

1.8 Details of Screening

The applicant should complete a screening checklist. This document will be assessed by the Authority upon application 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.

1.9 Individual patient data - statement of availability

Information should be provided were applicable.

1.10 Foreign Regulatory Status

Applicants are advised that this module should be completed for all applications (including those for multisource products).

1.10.1 List of countries in which an application for the same product as being applied for has been submitted, approved, rejected or withdrawn

The applicant should provide, in Module 1.10.1 of the dossier, a list of countries in which an application for the same product as being applied for has been submitted, approved, rejected or withdrawn, including dates of submission (if available).

Reasons for rejection or withdrawal should be provided.

If no application has been submitted for registration in the country of origin, include a statement to provide the reason for this decision.

1.10.2 WHO type CoPP

A copy of the WHO-type Certificate of a Pharmaceutical product should be submitted in this section.

1.10.3 Registration certificates or marketing authorisation

In the case of registration in the country of origin, or where a marketing authorisation has been granted by a NMRA of ICH, SADC and other countries that maybe recognised by individual SADC

MS, copies of the registration certificates or marketing authorisation should be supplied in this section.

1.10.4 Foreign prescribing and patient information

In the case of marketing authorisations in country of origin, or where marketing authorisation has been granted by the NMRA of ICH, SADC and others, countries that maybe recognised by Botswana MRA, copies of relevant PI/SmPC and PIL should be submitted in this section.

1.10.5 Data set similarities

Module 1.10.4 should contain a summary of the similarities / differences in the product submitted in ICH, SADC and other countries that maybe recognised by Botswana.

Module 2: OVERVIEWS AND SUMMARIES

Module 2 of the CTD dossier contains the summaries and overviews for the quality, non-clinical and clinical sections of the Dossier. For innovator products, the clinical overview should include a statement regarding Good Clinical Practice (GCP) compliance. In the case of generic medicines, the MRA may grant exemption from the submission of Non-clinical and Clinical Overviews and Summaries. As such, the following sections should be submitted:

2.1 Table of contents for Module 2
2.2 Introduction to the CTD submission
2.3 Quality Overall Summary through form ***BOMRA/ER/VET/P02/F02***

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 API, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

2.3 Quality Overall Summary (QOS)

The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD. 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.

2.4 Nonclinical 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.

2.5 Clinical 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.

2.6 Nonclinical 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.

2.7 Clinical 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 ACTIVE PHARMACEUTICAL INGREDIENT

The active pharmaceutical ingredient information can be submitted to Botswana Medicines Regulatory Authority in any one of the following options,

1. Certificate of Suitability (CEP) issued by the EDQM
2. Drug master file (DMF) or
3. Full details as outlined in Module 3.2.S1 to 3.2.S.7 below.

The applicant should thus clearly state at the beginning of the API section in the Product Dossier and in the Quality overall Summary, the format of the information of the Active substance from each API manufacturer.

Ref: EMA/CVMP/QWP/707366/2017

The submission packages for each option should include the following:

Option 1: CEP

If an applicant is using option 1, these requirements should be satisfied,

i. A complete copy of a valid CEP (and its annexures) should be submitted
ii. Declaration of Access for the CEP duly filled and signed by the CEP holder on behalf of the VMP manufacturer or applicant should be submitted
iii. A written commitment by the applicant, to
    a. submit an updated CEP in cases of any variations
    b. notify the Authority in the event of CEP withdrawal or lapse
    c. submit full API data in support of VMP registration in the event a CEP is withdrawn

Along with the valid CEP, the applicant should submit cGMP certificates for the API manufacturers in addition to the following,

iv. *3.2.S.1.3 General properties*: A discussion of any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section.
v. *3.2.S.3.1 Elucidation of structure and other characteristics studies:* information on identified polymorphs (except in cases where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.
vi. *3.2.S.4.1 Specification*: VMP manufacturer specifications including all tests and limits on the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.
vii. *3.2.S.1.2 / 3.1.S.4.3 Analytical procedures and validation* – for any tests not covered by the CEP and Ph.Eur. monograph.
viii. *3.2.S.4.4 Batch analysis:* results from three batches of at least pilot scale, demonstrating compliance with the VMP manufacturer's API specifications.
ix. *3.2.S.6 Container closure system*: specifications including descriptions and identification of primary packaging components, except in cases where the CEP specifies a retest period.
x. *3.2. S.7 Stability:* Except in cases where the CEP specifies a retest period that is the same as or of longer duration than the retest period proposed by the applicant.

NB. In the case of sterile active substances, data on the sterilization process of the active substance, including validation data, should be included in the VMP dossier

Option 2: DMF

Open parts of the DMF should be included in the VMP dossier. The applicant or VMP manufacturer should complete the following sections in the VMP dossier and Quality Overall Summary in accordance with the guidance provided unless otherwise indicated in the respective sections:

3.2. S.1 General information
3.2. S.2 Manufacture
3.2. S.2.1 Manufacturer(s)
3.2. S.2.2 Description of manufacturing process and process controls
3.2. S.2.4 Controls of critical steps and intermediates
3.2. S.3.2 Elucidation of structure and other characteristics
3.2. S.3.1 Impurities
3.2. S.4 Control of the active substance
3.2. S.5 Reference standards or materials
3.2. S.6 Container closure system
3.2. S.7 Stability

The API manufacturer should submit the restricted parts of the DMF directly to the Authority quoting the relevant product application number. It is the responsibility of the applicant to ensure that a complete DMF (open parts and the restricted parts of the DMF) is submitted to the Authority, and that they have access to the relevant information in the DMF concerning the current manufacture of their API.

DMFs structure should follow the format outlined for submission of API information in Option 3 below. As such, DMF holders should use the guidance provided for the option 3 below, when preparing their DMFs.

Option 3: Full API Details in VMP Dossier

The full API information, from chemistry, manufacture, quality control during manufacture, process validation etc. should be submitted in the VMP dossier as outlined in the sections below. The quality overall summary should also be completed in accordance with the outline given below.

3.2. S.1 General Information

3.2. S.1.1 Nomenclature

Full nomenclature of the API should be provided. This should include,

a. International Non-proprietary Name (INN),
b. Compendial name, *if relevant,*
c. Chemical name(s),
d. Company or laboratory code,
e. Other non-proprietary name(s) (e.g., national name, United States,
f. Adopted Name (USAN), British Approved Name (BAN)), and
g. Chemical Abstracts Service (CAS) registry number.

The listed chemical names should be consistent with those appearing in the scientific literature, and the product labelling information, that is, the prescribing information leaflet, the user information leaflet and the label.

3.2. S.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided. This information should be consistent with that provided in *Section 3.2. S.1.1.* For APIs that exist as salts, the molecular mass of the free base or acid should also be provided.

3.2. S.1.3 General Properties

A list of the physicochemical and other relevant properties of the active substance should be provided, particularly the physico-chemical properties that affect pharmacological efficacy and toxicological safety. This information helps to inform VMP formulation and manufacturing process development, and the choice of tests for release and stability purposes during the development of specifications.

The physical and chemical properties of the active pharmaceutical ingredient should be discussed including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile for target animals (e.g polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc (see table in the QOS). This list is not intended to be exhaustive but provides an indication as to the type of information that could be included.

Some of the more relevant properties to be considered for active substances are discussed below in greater detail.

3.2. S.1.3.1 Physical description

The description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.2. S.3.1 for further information on active substance solid forms).

3.2. S.1.3.2 Solubilities / quantitative aqueous pH solubility profile

The physiological pH range may differ from species to species. Data should be relevant to demonstrating an understanding of the in-vivo performance of the drug product as it relates only to the quality attributes.

The solubilities in a number of common solvents (e.g. water, alcohols, dichloromethane, and acetone), over the physiological pH ranges (pH 1 to 8) of the target animals in several buffered media should be provided in mg/ml.

If this information is not readily available from the scientific literature references or the DMF, it should be generated inhouse.

3.2. S.1.3.3 Polymorphism

Some new drug substances exist in different crystalline forms which differ in their physical properties. Generally, polymorphism is not a concern for APIs that are highly soluble under aqueous conditions or that are present in solution in the VMP product. If a polymorphic form has the potential to affect the quality or performance of the VMP in the targeted species, the submission should include detailed characterisation data of the API lot used in the manufacture of the Bio-batch. Physicochemical measurements and techniques are commonly used to determine whether multiple forms exist. Examples of these procedures are melting point (including hot-stage microscopy), solid state IR, X-ray powder diffraction, thermal analysis procedures (like DSC, TGA and DTA), Raman spectroscopy, optical microscopy, and solid-state NMR.

Below are the specific sections of the VMP Dossier where specific polymorphic data should be presented:

a. The polymorphic form(s) present in the proposed active substance should be listed in Section 3. S.1.1.3,
b. The description of manufacturing process and process controls (3. S.1.2.2) should indicate which polymorphic form is manufactured, where relevant,
c. The literature references or studies performed to identify the potential polymorphic forms of the active substance, including the study results, should be provided in Section 3. S.1.3.2.

Additional information is included in the referenced sections of this guideline.

3.2. S.1.3.4 Particle size distribution

Generally, particle size distribution is not a concern if the VMP is a solution or if the drug substance is dissolved during the drug product manufacturing process or is considered highly soluble in water. Particle size distribution of poorly soluble drugs may affect in vitro and in vivo performance of the VMP.

Although particle size distribution may be important for reasons related to VMP manufacturability and formulation performance, w.r.t other properties like content uniformity, the most important regulatory concern relates to the possible impact of particle sizes on the dissolution profile and subsequently the bioavailability and / or stability of the VMP in target species.

For poorly soluble drugs, the submission should appropriately characterize the particle size distribution of API batches used in comparative clinical or bioavailability studies. Further to that, a test for particle size distribution should be included in the API specification to ensure that commercial batches match the API batch or batches used in the manufacture of the Bio-batch. If a particle size distribution test is included in these specifications, it is recommended that limits be set for d10, d50, and d90.

Ref: ICH Q6A

3.2. S.2 Manufacture

3.2. S.2.1 Manufacturer(s)

The name, address, and responsibility of the facilities involved in the manufacturing, packaging, labelling, and testing of the active pharmaceutical substance should be provided. This applies to the production steps after introduction of the starting material(s). If certain facilities are responsible only for specific steps (e.g. milling of the active substance), this should be clearly indicated.

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 also 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 API should be provided.

3.2. S.2.2 Description of Manufacturing process and Process Controls

The description of the manufacturing process represents the applicant's commitment for the manufacture of the API. Information should be provided to adequately describe the manufacturing process and process controls. Alternate processes should be described and explained with the same level of detail as the primary process. It should be demonstrated that batches obtained by the alternate processes have the same impurity profile as the principal process. If the obtained impurity profile is different, it should be demonstrated to be acceptable according to the requirements described under 3.2. S.3.2. Reprocessing steps should be identified and justified. The Reprocessing method should be clearly described and the criteria for deciding when re-processing can be performed should be provided. Any data to support this justification should be either referenced or filed in 3.1. S.2.5. Emphasis should be placed on steps of the process having an impact on the quality of the active substance or intermediates and which are classified as 'critical' (see also under 3.2.S.2.4).

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

A graphical representation or flow diagram of the synthetic process(es) should be provided. This should include the reaction schemes that include chemical structures and molecular formulae of starting materials, intermediates and the active substance, as well as the reagents, catalysts and solvents used and identifying the operating conditions.

3.2. S.2.2.2 A sequential procedural narrative:

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of materials (starting materials, intermediates, solvents, catalysts and reagents and process aids) used in the current representative production scale batch. The narrative should describe each step in the manufacturing process, and identify critical steps, critical process parameters, process controls employed, and ranges for process parameters (e.g.: temperature, pressure, pH, time, flowrate, etc.). If a cross referenced DMF includes a detailed

description of the manufacturing process, the applicant need only to include a brief summary of the manufacturing process including a flow diagram representing the route of synthesis in the submission. The manufacturing process should start from simple, commercially available or well characterized starting materials. The description of the process should indicate the scale of manufacture and the range for which the considered process may be used. Yields or yield ranges for each stage should be provided.

As discussed in ICH Q7, the point at which the active substance starting material is introduced into the manufacturing process is the starting point of the application of GMP requirements, according to the above guideline. The API starting material itself needs to be proposed and justified by the manufacturer and accepted as such by assessors. The API starting material should be fully characterized with respect to identity and purity.

In addition to the detailed description of the manufacturing process as per ICH M4Q, the recovery of materials, if any, should be described in detail with the step in which they are introduced into the process. Recovery operations should be adequately controlled such that impurity levels do not increase over time. For recovery of solvents, any processing to improve the quality of the recovered solvent should be described. Regarding recycling of filtrates (mother liquors) to obtain second crops, information should be available on maximum holding times of mother liquors and maximum number of times the material can be recycled. Data on impurity levels should be provided to justify recycling of filtrates.

Where there are multiple manufacturing sites for one active substance, a comprehensive list in tabular form should be provided comparing the processes at each site and highlighting any differences. All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvents in the final steps of purification and/or crystallization is not recommended.

Where polymorphic/amorphous forms have been identified, the form resulting from the synthesis should be stated. Where particle size is considered a critical attribute (see 3.2. S.3.1 for details), the particle size reduction method(s) (milling, micronization) should be described. Justification should be provided for alternate manufacturing processes.

For sterile drug substances, the submission should include a complete description of the method of sterilization and the controls used to maintain sterility during storage and shipping. For drug substances produced by fermentation, the submission should contain additional information, including source and type of micro-organisms used, precursors, composition of media, details on how the reaction conditions are controlled (e.g., times, temperatures, rates of aeration), and name and composition of preservatives. For drug substances of plant origin, the submission should include a description of the botanical species and the part of plant used, the geographical origin, and the time of year of harvest, when relevant. The submissions should record the nature of chemical fertilizers,

pesticides, fungicides, and so on, if these have been employed during cultivation. It may be necessary to include in the drug substance specification limits for residues resulting from such treatments. The submission may also have to confirm the absence of toxic metals and radioactivity.
Ref: ICH Q7 and ICH M4Q

3.2. S.2.3 Control of Materials

Materials used in the manufacture of the active substance (starting materials, solvents, reagents, catalysts, process aids, etc.) should be listed identifying where each material is used in the process. Adequate specifications for these materials should be provided and should include an identification test. The specifications should address the characteristics of the material and its suitability for the intended use.

3.2. S.2.3.1 Biologically sourced materials:

Information on the source, processing, characterisation and control of all materials of biological origin (human or animal) must be provided, including viral and/or TSE safety data.

3.2. S.2.3.2 API Starting Material:

The ICH Q11 requirements in relation to the selection of starting materials are relevant to all active substances, regardless of the type of development approach.

The description of the synthetic process and the schematic synthetic process should include all the steps of the process, proceeding from the starting material(s) to the intermediates, and ultimately to the active substance. The full description of the process should cover all the synthetic steps critical to the quality of the active substance. As highlighted earlier in section 3.2. S.2.2.2 above, the use of starting materials marks the beginning of the description of the process and manufacture under GMP. An acceptable API starting material should

1. be a synthetic precursor of multiple (at least 2 synthetic steps) chemical transformation steps from the final active substance intermediate. Acids, bases, salts, esters and similar derivatives of the active substance, as well as the racemate of a single enantiomer active substance, are not considered final intermediates.
2. form a significant structural fragment into the structure of the active substance.
3. be well characterised isolated and purified substance with its structure fully elucidated including its stereochemistry (where applicable),
4. have well defined specifications that include among others one or more specific identity tests and tests and limits for assay, as well as, specified, unspecified and total impurities,

The marketing authorisation applicant should propose and justify which substance should be considered as the API starting material (API SM). Non-isolated compounds are not considered appropriate to be selected as starting materials.

The name and address of the starting material manufacturers should be provided for each starting material. If there are several manufacturers for a single starting material, it should be clarified whether the starting material obtained from the different sources is prepared by the same route of synthesis or not. N.B. Specifications proposed for the starting material should apply to the material from each source.

Relevant viral safety and / or TSE data must be provided if any animal-derived material is used during the active substance manufacturing process (e.g. arising from fermentation, enzymes, amino acids, etc.).
Ref: ICH Q11

Materials of plant Origin: Information on the source, processing, characterisation and control of starting materials of plant origin must be provided to ascertain suitability. A contaminant profile should be established and submitted. Information on the scientific name (genus, species, variety and author) of the plant and plant part used should be specified, as should the solvents in the extraction process. Potential presence of foreign matter, pesticides, microbiological contamination, total ash, heavy metals, mycotoxins, radioactive contamination, residual solvents, and other relevant impurities should be discussed. Information on the geographical origin, collection or cultivation, harvesting, and post-harvest treatments (possible pesticides and fumigants used and possible radioactive contamination) may be appropriate depending on the subsequent synthetic steps.

Solvents, Reagents and other materials:
Specifications for all materials (solvents, reagents, catalysts, processing aids etc.) used in synthesis should be submitted. NB. Materials used in the final stages of the active substance synthesis may require greater control (i.e.: tighter specifications) than those used in earlier stages.
Ref: ICH Q6A

3.2. S.2.4 Control of Critical Steps and Intermediates

3.2. S.2.4.1 Critical Steps:

Tests and acceptance criteria performed at critical steps identified in 3.2. S.2.2 of the manufacturing process should be described and justified based on relevant experimental data. 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 API meets its specification.

The critical steps could be, for instance: mixing of multiple components, phase change and phase separation steps, steps where control of temperature and pH are critical, steps which introduce an essential molecular structural element or result in a major chemical transformation, steps which introduce (or remove) significant impurities to (or from) the API. For those impurities not controlled in the API, suitable in-process controls should be carried out with justified ranges and documented. Also, a critical step could be the final purification step.

Steps which have an impact on solid-state properties and homogeneity of the active substance are generally considered as critical, particularly, if the active substance is used within a solid dosage form, since they may adversely affect dissolution of the active substance from the dosage form and thereby affect bioavailability. Proper justification should be provided when these properties do not impact performance of the finished product.

3.2. S.2.4.2 Intermediates:

Information on the quality and control of intermediates isolated during the process should be provided. If non-compendial methods are used to control the intermediate(s), they should be suitably validated. Validation data is not expected unless the test in question is essential for the control strategy of the active substance (e.g. removal of a mutagenic impurity). Information on the characterisation of these intermediates should be provided.

3.2. S.2.5 Process Validation

It is expected that the manufacturing processes for all active substances are properly controlled before commercialisation, even though no process validation data is provided in the application. In the case of a sterile API, validation of the sterilisation process is a requirement. Process validation data and/or evaluation studies for aseptic processing and sterilisation should be provided. The controls used to maintain the sterility of the active substance during storage and transportation should also be provided. Alternate processes should be justified and described (see guidance in 3.2. S.2.2 for the level of detail expected).

3.2. S.2.6 Manufacturing Process Development

A description and discussion of any significant changes made to the manufacturing process and/or manufacturing sites of the active substance used in producing non-clinical, clinical, scale-up, pilot, and, if available, production scale batches, should be provided. Reference should be made to the active substance data provided in section 3.2. S.4.4.

For existing APIs, all provided data might be obtained on production scale batches manufactured according to the presented manufacturing description. A description of the manufacturing process development is not necessary in these cases but will often add to the understanding of the control strategy.

3.2. S.3 Characterisation

3.2. S.3.1 Elucidation of Structure and other Characteristics

This section ordinarily describes the information which is expected for a new chemical entity. For active substances that are not described in an officially recognized pharmacopoeia, a scientific discussion of the chemistry of the active pharmaceutical substance should be provided, including unequivocal proof of structure, configuration and potential isomerism. This should include a presentation of the stereochemical properties of the molecule. The studies carried out to elucidate

and/or confirm the chemical structure should normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectrometry (MS), Xray powder diffraction (XRPD) and differential scanning calorimetry (DSC). It is important that the evidence of structure should be related to the actual material to be used in the marketed product, especially for highly complex molecular structures. The evidence should comprise, the results, interpretation of the results and a discussion of the results.

The physico- chemical characteristics to be elucidated are as outlined in section 3.2. S.1.3 above. Relevant results described in this section should be reflected in the control tests on the active substance to check batch-to-batch uniformity.

If the data included in this section originates from a synthetic process other than the one covered by the application (i.e. different routes), evidence may be required to confirm the structural identity of the materials from different origin. This is particularly important where toxicological studies have been carried out on material from different origin.

Ref: ICH Q6A

3.2. S.3.2 Impurities

Information on impurities should be provided. These include related substances, residual solvents, elemental impurities, reagents and those derived from reagents. The related substances considered as actual or potential impurities arising from the synthesis and degradation products should be described and discussed briefly including an indication of their origin, regardless of whether a pharmacopoeial standard is claimed. Thus, the discussion should not be limited to impurities specified in the active substance monograph. Also, it should cover all potential impurities of the starting materials, by-products, intermediates, and degradation products. It may be presented in a table, that list each potential impurity, the name, chemical structure, and its origin (e.g., synthetic intermediate, by-product, residual solvent from crystallization step).

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification of the impurities should be determined based on potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the active substance. For active substances available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed.

The mutagenic potential of impurities should be addressed. In each case, it should be stated whether actual samples of impurities have been synthesized or isolated for test purposes. Structural analysis data for identified impurities should be provided unless identity is proved by other means. Possible routes of degradation should also be discussed - please see section 3.2. S.7.1.

The analytical methods (with limits of detection (LOD) and limits of quantitation (LOQ) used to detect each of the likely impurities considered above or other related impurities, the exact identities of which may be unknown, should be described. Copies of relevant chromatograms should be

provided. A summary should be given on the nature and levels of the actual impurities detected in the batch samples of the material. Justification should be provided for selecting the limits based on safety and toxicity data, as well as on the methods used for the control of impurities (see 3.2. S.4.4.). For qualification of impurities, refer to 3.2. S.4.5

Ref: VICH GL10(R), VICH GL11(R) and VICH GL18(R)
As read with ICH Q3A, Q3B and Q3C

3.2. S.4 Control of the Active Pharmaceutical Ingredient

3.2. S.4.1 Specifications

The API manufacturer's, together with VMP manufacturer's API release and shelf-life specifications should be provided. At release, the following tests should be performed as a minimum: Description, Identification, Impurities, Assay and/or potency. Additional tests may be required depending on the nature of the active substance or its subsequent use (e.g. polymorphic form, enantiomeric purity, particle size, microbiological purity, bacterial endotoxins, etc). Appropriate acceptance criteria (numerical values / ranges where applicable) and reference standards should be specified for each test. The API specifications should be version controlled, signed and dated by the responsible QA or designate.

Ref: VICH GL39 as read with ICH Q6A

3.2. S.4.2 Analytical Procedures

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

The version (e.g. code number/version/date) and the reference standard (e.g. BP or inhouse) of the Analytical Procedure should be provided for version control purposes. For each test parameter, the analytical method used should be specified (e.g. Identification by IR, UV, HPLC or laser diffraction).

3.2. S.4.3 Validation of Analytical Procedures

Analytical method validation data, in the form of validation protocols and reports, including experimental results for the analytical procedures used for the control of the active 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 API Quality. All non- pharmacopoeial methods should be validated according to the requirements of the current guidelines. It is the responsibility of the manufacturer/applicant to ensure that control of the API is performed in accordance with updated technologies, in the event of very old monographs.

Ref: VICH GL1 and VICH GL2 as read with ICH Q2 (R1)

3.2. S.4.4 Batch Analyses

A description of batches and results of batch analyses should be provided. 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 analytical tests, and uses of the batches. It should be stated whether the API batches in question were used for the manufacture of comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scaleup and, if available, commercial scale batches.

For new chemical entities, the batch analyses data should also include API batches used in the pre-clinical tests and clinical studies reported in support of the application. In the case of generic VMPs, batch analyses data from at least three batches of at least pilot scale from each proposed manufacturing site of the active substance and including the batch(es) used in the comparative bioavailability or biowaiver studies should be submitted. The data should be presented in a tabular format for improved clarity.

CoAs from the API manufacturer(s) for at least three recent consecutive batches from each manufacturing site, manufactured according to the proposed process at not less than 10% of maximum production scale batch at the time of submission should be provided. In addition, CoAs from the VMP manufacturer for at least two batches from each proposed manufacturing site of the active substance, including the batch(es) used in the comparative bioavailability or biowaiver studies should also be submitted. These results should demonstrate that routine production material falls within the specification limits cited for the purpose covered by the marketing authorisation.

Quantitative test results should be expressed numerically e.g. impurity levels. Results which only state that the material "complies" with the test are insufficient. The batch analyses should include all the tests in the specification. There may, however, be cases where previous batches were tested using a slightly different specification. In these cases, a brief explanatory note should be included. Any apparently inconsistent or anomalous results in the batch analyses should be discussed.

3.2. S.4.5 Justification of Specifications

Justification for the choice of test parameters, test procedure, and acceptance criteria considered in the API specification should be provided. The justification of the specification should be based on results from preclinical, clinical and/ or development pharmaceutics data. This should take into account the qualification of impurities and the overall VMP quality control strategy. Additional tests, (e.g., impurity tests) might be necessary for APIs that are not described in a pharmacopoeia, and impurity levels above the VICH GL10 qualification thresholds require toxicological evaluation.

For API described in recognised international pharmacopoeia, the respective monograph of the pharmacopoeia should be the basis of the active substance specification.

Ref: VICH GL10

As read with ICH Q3A, Q3B and Q3C

3.2. S.5 Reference Standards

Information on the reference standards or reference materials used for testing of the active 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, assay 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., BP,) where one exists, and the lot number should be provided. Where a pharmacopoeial standard is claimed for the API, the primary reference standard from the claimed pharmacopoeia used. Pharmacopoeial reference substances are qualified as primary reference standards and do not need to be further qualified, provided they are used for their intended purpose.

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, impurities profile, 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. Reference standards should normally be established for specified impurities. Refer to section 3.2. S.4.2 for additional guidance.
Ref: ICH Q6A

3.2. S.6 Container Closure

A brief 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 active substance, its suitability should be justified. Depending on nature of the active substance, aspects that may need justification include choice of the primary packaging materials, protection from light and/or moisture, compatibility with the active substance including sorption to material and leaching and/or any safety aspects of materials of construct. NB. Primary packaging components are those that are in direct contact with the API.

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 (e.g. polyethylene bag) and secondary packaging (e.g. fibre or metal drum).

3.2. S.7 Stability

3.2. S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions (light stress, higher temperature, etc.), as well as conclusions with respect to storage conditions and retest date or Shelf-life as appropriate.

Evidence of how the quality of an API varies with time under the influence of a variety of environmental factors such as temperature, humidity and light should also be provided.

3.2. S.7.1.1 Stress testing

Stress testing should be carried out on a single batch of the API. Stressing the active substance can help to identify the potential degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual active substance involved. Degradation paths for pharmaceutical compounds are typically reactions of hydrolysis, oxidation, photolysis, and/or acid/base chemistry. To force these reactions, the active substance is placed in solution, for example, under the conditions shown in the following table.

Stress Factor	Condition
Heat	60 °C
Humidity	75% RH or greater
Acid	0.1N HCl
Base	0.1 N NaOH
Oxidative	3% H_2O_2
Photolytic	Metal halide, Hg Xe Lamp or UV -B/Fluorescent light
Metal irons(optional)	0.05 M Fe^{2+} or Cu^{2+}

The objective is not to completely degrade the API, but to generate degradation to a small extent, typically 10-30% loss of active by assay when compared with non-degraded compound. In the total absence of degradation products after 10 days, the active substance is considered stable. If degradation is detectable but its extent is less than 10%, then the stress factors or the stress conditions, or both, should be increased. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in VICH GL5. Solid state degradation can also be considered. For active substances, placing a solid sample at elevated temperatures e.g. 60-120 °C, or 5-10 °C below the melting point— can generate some degradation compounds.

This approach serves to generate degradation products, which are not ordinarily generated under accelerated conditions, which can be used as the worst case to validate suitability of the analytical procedures.

For active substances not described in an official pharmacopoeia monograph, there are two options:

- When available, it is acceptable to provide the relevant data published in the "peer review" literature to support the proposed degradation pathways.
- When there is no scientific literature available in the public domain, including official pharmacopoeias, stress testing should be performed.

Ref: VICH GL5

3.2. S.7.1.2 Accelerated and long-term testing

The applicant should summarize the stability testing program and report the results of stability testing of not less than three (minimum one production scale and two pilot scale) batches of the active substance. The results for each test parameter should be discussed, the trends analysed, and a retest date proposed.

Information on the analytical procedures used to generate the data and validation of these procedures should be included. The applicant should describe the methods used during stability studies; if this is identical to methods described elsewhere in the dossier, cross-referencing will suffice. If different methodology was used, provide validation of tests for impurities (including degradants), assay and for other tests, as necessary.

NB: Unless otherwise justified, 40 ± 2°C/75 ± 5% RH, and 30°C ± 2°C/65± 5%RH are the accelerated (6 months) and long-term stability conditions. A storage statement should be proposed for the labelling (if applicable), which should be based on the stability assessment of the active substance. A retest period should be derived from the stability information, and the approved retest date should be displayed on the container label and CoA.

For drug substances intended for storage in a refrigerator, at least 6 months accelerated, and 12 months long-term stability data generated at 25°C ± 2°C/60% RH ± 5% RH and 5°C ± 3°C respectively, should be submitted.

If significant change occurs between 3- and 6-months' testing at the accelerated storage condition, the proposed re-test period should be based on the real-time data available at the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g., during shipping or handling. This discussion can be supported, if appropriate, by further testing of a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

For drug substances intended for storage in a freezer, the re-test period should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing of 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.

3.2. S.7.2 Post Approval Stability and Stability Commitments

A post-approval stability protocol and stability commitment should be provided if data for production scale batches covering the full proposed re-test period or Shelf-life is not available.

3.2. S.7.3 Stability Data

Detailed results of the stability studies including forced degradation studies and stress conditions should be presented in an appropriate tabular or graphical format. Information on the analytical procedures used to generate the data and validation of these procedures should be included. The major degradation pathways of the active substance should be discussed. The storage conditions and the retest period should be defined. All quantitative tests (e.g. individual and total degradation product tests and assay tests), should be reported in actual numerical values rather than vague statements such as "within limits" or "conforms".

Ref: VICH GL3(R), VICH GL58, VICH GL45, VICH GL5 and VICH GL51
As read with ICH Q1 A (R2)

3.2. P VETERINARY MEDICINAL PRODUCT

3.2. P.1 Description and Composition of the VMP

The VMP submission should include the following:

3.2. P.1.1 Description of the dosage form

A description of the VMP intended for marketing in Botswana should include the pharmaceutical, the strengths, 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.

3.2. P.1.2 Composition

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. mg per tablet, mg per ml, mg per vial), including the overages if any, the function of each component(e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative), the reference standard for each (e.g. BP, House) and percentage composition should be provided.

If the VMP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated, and all overages should be declared and the justification for inclusion of the overages in the formulation should be provided.

Component and quality standard (and grade, if applicable)	**Reference Standard**	***Name of the VMP (including strength/dose and dosage form)***	
		Function	**Quantity per unit (mg)**

N.B. The table can be adapted to show composition of different parts of the formulation e.g. core tablet and film coating.

3.2. P.2 Pharmaceutical 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 a VMP are appropriate for the purpose of the said VMP should be provided in this section of the submission. These studies described here are distinguished from routine control tests conducted according to the specifications. VMP manufacturer should identify and describe all the formulation and process attributes (critical parameters) that can influence batch reproducibility, VMP performance and quality. Supportive data and results from specific studies or published literature can be included.

At a minimum, Pharmaceutical 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, bioavailability, strength and stability
- identification of potential critical quality attributes (CQAs) of the VMP, so as to adequately control the product characteristics that could have an impact on quality
- a discussion of the potential CQAs of the active substance(s), excipients and container closure system(s) including the selection of the type, grade and amount to deliver drug product of the desired quality

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

Ref: EMEA/CVMP/315/98 As read with ICH Q6A, ICH Q8 (R2), ICH Q9 and ICH Q10.

3.2. P.2.1 Components of the VMP

3.2. P.2.1.1 Active Pharmaceutical Ingredient

The compatibility of the active substance with excipients listed in 3.2. P.1, and in the case of fixed dose combinations, the compatibility of active substances with each other, should be provided. In addition, key physico-chemical characteristics (e.g., water content, solubility, and particle size distribution, polymorphic or solid-state form) of the active substance(s) that can influence the manufacturability, performance and quality of the VMP should be discussed.

In addition to the visual examination, chromatographic results (assay, purity) are required to demonstrate active substance - active substance and active substance - excipient compatibility. Generally, active substance-excipient compatibility data is not required for excipients demonstrated to be present in the reference product (e.g. by way of SmPC).

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 VMP should be discussed, relative to their respective functions. Excipient – excipient compatibility should be discussed. Where novel excipients are used, full information on composition and function of the excipient 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 Pharmaceutical Product (VMP)

3.2. P.2.2.1 Formulation Development

The therapeutic activity, posology and route of administration and proposed usage of the product should be taken into consideration when designing the formulation of a VMP. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed, where appropriate. For established generic products, that is, one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years, Formulation Development may not be required.

Liquid and Semi Solid Formulation:

The concentration of the key components (antimicrobial preservatives, antioxidants, surfactants, solvents, chelators, permeability enhancers and release modifiers 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 positive and 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 VMPs administered intravenously. This includes physical and chemical compatibility with recommended diluents and materials of construct of administration apparatus for the recommended or anticipated period.

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 pharmaceutics should address particle size, ease and rate of dissolution and homogeneity, if applicable. Chemical and physical stability over duration of use of the VMP should be addressed. Due to microbiological consideration, in-use shelf life should not exceed 24 hours.

Homogeneity is a critical quality attribute / parameter for solid dosage forms. Differences in surface properties, crystallinity, particle size etc. may result in segregation of powders in dry mixes. Thus, homogeneity of the formulation should be addressed at the development stage and confirmed during the validation of the manufacturing process.

Performance of solid dosage forms is a function of disintegration and dissolution of the formulation. As such, disintegration properties of each finished batch of OSD and pessaries, or at intermediate stages e.g. uncoated core tablets or other dose forms prior to final coating should be studied. Routine performance of a disintegration test may not be necessary if dissolution test with acceptable discriminatory power is included in FPP specification. The actual amount of an API liberated from the dosage form into an aqueous reservoir in-vitro is intended to reflect the in-vivo behaviour of the VMP. Although in-vivo behaviour depends on a number of factors, dissolution test provides useful range of data, and it should be performed for all solid dosage forms at development phase and stability studies in order to establish whether such testing would need to be included routinely in the FPP specification.

For Premixes intended for medicated feeding stuffs for veterinary use and powders/granules for oral use or use in drinking water, refer to EMEA/CVMP/199/97. For modified release preparations, choice of dissolution test conditions and release rates adopted for assessing batch reproducibility needs to

be justified. Refer to EMA/CHMP/QWP/428693/2013: Guideline on quality of oral modified release products for more information.

Other Formulations:

Injection: this is the VMP dosage form that is largely used as multidose preparations. It is usually not based on aqueous, but frequently on oily or other non-aqueous media. Use and level of microbial 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.

Teat dips & sprays: these are ready to use and are usually concentrates which are diluted prior to use. Thus, pharmaceutical development for these, should address stability and acceptability of storage recommendations of diluted products.

Dips: due to their special way of use, initial concentration, subsequent replenishments, stripping studies and stability of diluted products should be addressed.

Other preparations will be treated on a case by case basis.

3.2. P.2.2.2 Overages

Addition or inclusion of overages in the formulation of VMPs is generally discouraged due to the potential risk of overdosing. Any added overages should be justified. Where the justification for added overages is to compensate for API loses during manufacturing, the manufacturing steps where loses occur should be identified, and the reason for the loses discussed. Evidence of API loss should be in the form of batch analyses results prior and post each alleged manufacturing step. Overages for the sole purpose of extending shelf-life or compensating for API loses during shelf life is not acceptable. Otherwise, the only acceptable justification would be safety and efficacy data from well-designed clinical studies. NB. It is better to reduce the shelf-life than to risk exposing the animals to excessive API dose.

3.2. P.2.2.3 Physicochemical and Biological Properties

Parameters relevant to the performance of the VMP, such as pH, dissolution, redispersion, particle size distribution, aggregation, rheological properties, should be considered during pharmaceutical development studies. For Parenteral VMPs, factors such as tonicity, globule size of emulsions, particles size and shape as well as changes in the crystal form, 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 controls for the VMP. For sterile parenteral, ophthalmic or topical preparations, an appropriate method of sterilisation should be chosen, and the choice justified. Ordinarily all such products should be terminally sterilised in their final CCS (intended for marketing), using a fully validated terminal sterilisation method (using steam, dry heat or ionising radiation). Where terminal sterilisation is not possible, aseptic processing may be considered provided it is fully and scientifically justified. Heat lability of active substance or excipient is considered acceptable justification. For heat stable products, heat lability of the CCS should not in itself be considered as adequate justification for not utilising terminal sterilisation.

In the event a different manufacturing process, from the process described in 3.2. P.3.3, was used to produce comparative bioavailability or biowaiver batches, a discussion should be provided together with comparative results of the VMP 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 VMP, 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 VMP 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 VMPs e.g. dropper pippetes, drenching guns, oral syringes or pour-on measuring device etc.).

The justification should take into consideration the safety to the user and target animals, possibility of 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 VMP. 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 API, and other 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 VMP. 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 VMPs, evidence should be provided that a reproducible, and accurate dose of the VMP 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. For single dose units, such as intramammary preparations, expelled volume or weight should be considered instead of fill volume or weight.

Fragmentation and /or self sealability: For all multidose vials where the same vials could be used for a wide range of 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 VMP 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 limit 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 antimicrobial agent (preservative) should be justified and verified by appropriate studies (e.g. Ph. Eur. general chapters on antimicrobial preservatives) using a batch of the VMP. 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 VMP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria. A single primary stability batch of the VMP 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 VMP with reconstitution diluent(s) or dosage devices (e.g., precipitation of active 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 should be demonstrated with respect to the principal VMP 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).

3.2. P.3 Manufacture

3.2. P.3.1 Manufacturer

The name, address, and responsibility of each of the facilities involved in the manufacturing, packaging, labelling, and testing of the VMP should be provided. In the case, of sterile powders for injections, where a sterile API is just aseptically packed into the CCS, the facility involved in the API sterilisation should be included, as it is considered part of VMP manufacturing process. For all other formulations, blending of the API with the excipient(s) is considered the first step in the VMP 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 evidence of registration (CoPP or registration certificate) issued by the competent authority in the country of manufacture of the VMP should be provided to demonstrate that the VMP is manufactured and registered for use in the country of origin. VMPs should be registered in accordance with national requirements in the country of origin or country of manufacture. In cases where a VMP 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. BoMRA 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. mg per tablet, mg per ml, mg per vial) and per batch (e.g. kg/L for each proposed batch size), including the overages if any, the function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative), the reference standard for each (e.g. BP, In-House) and percentage composition should be provided.

If the VMP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated, and all overages should be declared and the justification for inclusion of the overages in the formulation should be provided.

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)	**Standard**	***Name of VMP (including strength and dosage form)***											
		Function	**Quantity per unit (mg)**	**%**	**Quantity per clinical batch (kg/L)**	**%**	**Quantity per validation batch (kg/L)**	**%**	**Quantity per stability batch (kg/L)**	**%**	**Quantity per production batch (kg/L)**	**%**
e.g. Oxytetraxycline trihydrate	*IH*	*Active*	*200*	*20*	*2*	*20*						

N.B. sizes and use of each batch should be declared. The table can be adapted to show composition of different parts of the formulation e.g. core tablet and film coating.

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

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 VMP controls should be provided. In addition, a narrative description of the key steps in the manufacturing process, packaging and 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 VMPs, where necessary. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3.2. P.2.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

The intermediate product holding time should be supported by the submission of stability data, if longer than 30 days. Maximum cumulative hold time from date of API-excipient mixing to primary packaging should not exceed 90 days. Ideally, batch processing should be completed within 30 days from the first date on which the API is mixed with Excipients. 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 referenced or filed in this section (3.2. 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, terminal sterilization etc.

Ref: ICH Q8, Q9, Q10

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 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria, and the justification including experimental data performed at the critical steps identified in 3.2. P.3.3 of the manufacturing process, to ensure that the process is controlled, should be provided.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

Below are some of the examples of applicable in-process controls:

- Granulations: moisture (limits expressed as a range), blend uniformity (e.g. low dose tablets), bulk and tapped densities, particle size distribution.

- Oral solid dosage forms: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating.
- Liquid preparations: pH, specific gravity, clarity of solutions; and
- Parenteral preparations: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules etc.

Ref: VICH GL1 and VICH GL2
As read with ICH Q6A, Q8, Q9, Q10,

3.2. P.3.5 Process Validation and/or Evaluation

Process validation should be conducted on all drug products, but the registration requirements differ depending on whether the VMP is sterile or nonsterile.

3.2. P.3.5.1 Non-sterile VMPs:

The process validation data package should include,

a) a copy of the process validation protocol, specific to this VMP. The protocol should include:

- a reference to the current master production document,
- a discussion of the critical equipment,
- the process parameters that can affect the quality of the VMP (critical process parameters (CPPs)) including challenge experiments and failure mode operation,
- details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender/storage bins for uniformity testing of the final blend),
- the testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies,
- the analytical procedures and acceptance criteria,
- the methods for recording/evaluating results; and
- the proposed timeframe for completion of the protocol.

b) a commitment that three consecutive production scale batches of this VMP will be subjected to prospective validation in accordance with the above protocol; The applicant should submit a written commitment that information from these studies will be available for verification by the Authority, or

c) If the process validation studies have already been conducted (e.g. for sterile products), a copy of the process validation report should be provided in the dossier.

As part of the process validation, some studies may be conducted on pilot scale batches if the process has not yet been scaled up to production scale. It should be noted that pilot batch size should correspond to at least 10% of the production scale batch (i.e. such that the multiplication factor for the scale-up factor does not exceed 10). For solid oral dosage forms this size should generally be 10% of the maximum production scale or 100,000 units whichever is the greater. Where the intended

batch size is less than 100,000 units, the predictive value of the pilot batches may be limited, and a justified approach should be followed. For other dosage forms the pilot batch size should be justified taking into account the risk to the patient, in the event of failure of the dosage form.

3.2. P.3.5.2 Sterile VMPs:

Just like, for the non-sterile products, a copy of the process validation protocol identifying the critical steps, equipment, and process parameters that can affect the quality of the drug product, and define testing parameters, sampling plans, analytical procedures, and acceptance criteria, and a validation report, should be included in the dossier at submission of the application for registration of the VMP. It should be noted that, the manufacture of sterile VMPs needs a well-controlled manufacturing area (in terms of strictly controlled environment, highly reliable procedures and appropriate in-process controls). Thus, a detailed description of these conditions, procedures and controls should be provided, together with actual copies of the following standard operating procedures:

i. Washing, treatment, sterilizing and depyrogenation of containers, closures and equipment
ii. Filtration of solutions
iii. Lyophilization process
iv. Leak test of filled and sealed ampoules
v. Final inspection of the product; and
vi. Sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of sterile parenteral VMPs. The process can make use of moist heat (e.g. steam), dry heat, filtration, gaseous sterilization (e.g. ethylene oxide), or radiation. It should be noted that terminal steam sterilization, when practical, is considered the method of choice to ensure sterility of the final VMP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence, in the form or validation results, should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the VMP will not be affected. Details such as F_0 range, temperature range and peak dwell time for a VMP and the container closure should be provided. Although standard autoclaving cycles of 121°C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should demonstrate control of the levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, absence of extractable and lack of adsorption of the active substance or any of the components. Filter integrity or challenge test using appropriate microorganism spiked media should also form part of filter validation. For the validation of aseptic filling of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling ampoules with culture

media under normal conditions, followed by incubation and QC for microbial growth. A level of contamination of less than 0.1% is considered acceptable.

Ref: EMA/CHMP/CVMP/QWP/749073/2016 as read with ICH Q8, Q9, Q10

3.2. P.4 Control of Excipients

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 VMP (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 pharmacopoeia 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.

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 FDA "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.

For flavours the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. USA or EU). If additional purification is undertaken on commercially available excipients details of the process of purification and modified specifications should be submitted.

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

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

Copies of analytical method validation information are generally not submitted for the testing of excipients, with the exception of 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). The following excipients should be addressed in this section: gelatine, phosphates, stearic acid, magnesium stearate and other stearates. If the excipients are from plant origin a declaration to this effect will suffice.

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 should be provided. Materials of animal origin should be avoided whenever possible. Where available, a CEP demonstrating TSE compliance should be submitted. In this case, a complete copy of the CEP (including any annexes) should be provided.
Ref: ICH Q5A, Q5D, Q6B.

3.2. P.4.6 Novel Excipients

For excipient(s) used for the first time in a VMP 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 VMP format.

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

3.2. P.5.1 Specifications

The proposed release and shelf life specifications for the VMP should be provided. As defined in ICH's Q6A guideline, a specification is: "a list of tests, references to analytical procedures [officially recognized compendial standard e.g. Ph. Eur., or In-House (manufacturer's) standard] and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. Specifications establish the criteria to which a VMP should conform to be considered acceptable for its intended use. They are critical quality standards that are proposed and justified by the manufacturer.

Copies of the VMP release and shelf-life specifications, which should be version controlled, signed and dated by the responsible QA or designate, should be provided in the dossier (VICH GL39). Tests for product appearance, identity and assay of the medicinal ingredients, and determination of degradation products are standard for all dosage forms. The other* tests to be included in the specification will depend on the dosage form and route of administration.

Table A: Guidance on other* test requirements for solid dosage forms

A. SOLIDS																						
Test	Tablet		Capsule		PFI		OFDT		Pessary		Implant		TP		Collars		IRD		Additive - H_2O		Additive-Feed	
	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL
Dimension									√	√	√	√			√	√						
Disintegration	√	√	√	√			√	√	√	√	√	√					±	±			±	±
Dissolution	±	±	±	±	√	√			±	±	±	±					±	±	±	±		
BET					±	±																
Friability	±	±	±	±					±	±	±	±					±	±				
Hardness	±	±							±	±	±	±					±	±				
Moisture content	±	±	±	±	±	±	√	√	±	±	±	±	±	±			±	±	±	±	√	√
Particle size			±	±	±	±							±	±					±	±	±	
Sterility					√	√					√	√										
Dose uniformity	±	±	±	±	±	±	±	±	±	±	±	±					±	±	±	±		
Weight uniformity	√	√	√	√	±	±	√	√	√	√	√	√					±	±	±	±	±	±
Average weight	√	√	√	√	±	±	√	√	√	√	√	√			√	√	√	√	±	±	±	±

Key: R – release, SL – Shelf-life, PFI – Powder for injection, OFDT – Oral freeze-dried tablet, TP – Topical powder and IRD – intraruminal device.

√ - the test should always be performed,

± - the test may/may not be performed. Justification should always be provided for the choice made.

Table B: Guidance on other* test requirements for semi-solid dosage forms

B. SEMI-SOLIDS												
Test	Cream		Gel		Paste		Topical Ointment		Eye Ointment		Intramammary	
	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL
Expressed weight	±	±	±	±	±	±	±	±	±	±	√	√
Microbial limits	√	√	√	√	√	√	√	√				
Particle size	±	±	±	±	√	√	±	±	√	√	√	√
Sterility									√	√	√	√
Dose uniformity					±	±			√	√	√	√
Viscosity	±	±	±	±	±	±	±	±	±	±	±	±

Table C: Guidance on other* test requirements for non-solid dosage forms

C. NON-SOLIDS																						
Test	Aerosol		AP		NAP		Eye drops		Intramammary		Oral solution		Oral suspension		Pour-on		Spot-on		Teat dip		Additive -H_2O	
	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL	R	SL
Discharge rate	√	√																				
Spray pattern	√	√																				
BET			±	±	±	±																
Sterility			√	√	√	√	√	√	√	√												
Expressed vol. uniformity			±	±	±	±			√	√	±	±	±	±			±	±			±	±
Head space oxygen	±	±	±	±	±	±																
Internal pressure	√	√																				
Microbial limits	±										√	√	√	√	±	±	±	±	±	±	±	±
Moisture content	±	±			±	±			±	±					±	±	±	±				
Particle size	±	±	±	±	±	±	±	±	±	±			√	√	±	±						
Particulate matter			√	√	√	√	√	√														
pH	±	±	√	√	±	±	√	√	±	±	√	√	√	√	±	±	±	±	√	√	√	√
Resuspendability			±	±	±	±							√	√	±	±						
Syringeability			±	±	±	±			±	±												
Uniformity of content			±	±	±	±	±	±	√	√	±	±	±	±			±	±			±	±
Viscosity					√	√			±	±			±	±	√	√			±	±		

Key: R – release, SL – Shelf-life, AP – Aqueous parenteral and NAP – Non aqueous parenteral.
√ - the test should always be performed,
± - the test may/may not be performed. Justification should always be provided for the choice made.

For all formulations, the following tests are applicable to both release and Shelf-life specifications, unless specified.

1. Appearance
2. Assay for the Active substance
3. Assay for chemical/antimicrobial preservatives (where applicable)
4. Impurities/degradation products

Proposed limits for degradation products that exceed the VICH qualification threshold of 1.0% can be qualified by comparison with the reference as discussed in the VICH GL11. Unless there is appropriate justification, the acceptable limit for the active substance content of a VMP in the release specifications is ± 5% of the label claim (i.e. 95.0105.0%).

Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified. Note that such differences for parameters such as dissolution are normally not accepted.

Ref: VICH GL39 and VICH GL 11
As read with ICH Q3B, Q3C, Q6A

3.2. P.5.2 Analytical Procedures

Details of the analytical procedures used for testing the VMP should be provided. They should be described with sufficient details to ensure that they can be repeated by any other accredited

Laboratory responsible for testing medicines. 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. Identification by IR, UV, HPLC or laser diffraction). 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 the justification provided.

Ref: VICH GL39 and VICH GL 11
As read with ICH Q3B, Q3C, Q6A

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 analytical procedures used for the control of the VMP, should be provided unless the methods are Pharmacopoeial, and the manufacturer/applicant have demonstrated that the stated Pharmacopoeial methods are suitable for controlling their VMP Quality (verification).

The compendial methods, as published, are typically validated based on an active substance or a VMP originating from a specific manufacturer. Different sources of the same active substance or VMP can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore, the monograph and compendial method(s) should be demonstrated suitable for the control of the proposed VMP.

The key analytical procedures used for determination of the assay, related substances and dissolution of the VMP 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, accuracy 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.

If an officially recognized compendial standard is claimed and an inhouse method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the inhouse and compendial methods should be demonstrated. This could be accomplished by performing duplicate analyses of one sample by both methods and providing the results from the study. For related compound methods, the sample analysed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

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.

Ref: VICH GL1 and VICH GL2 as read with ICH Q2 (R1)

3.2. P.5.4 Batch Analysis

A description of batches and results of batch analyses should be provided. 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 analytical tests, and uses of the batches. It should be declared whether the VMP batches in question were used for comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scaleup, or if available, commercial scale.

Analytical results tested by the company responsible for the batch release of the VMP (if different from the VMP manufacturer) should be provided for not less than three batches analyses. The testing results should include the batch(es) used in the comparative bioavailability or biowaiver studies. 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).

Ref: VICH GL39 and VICH GL 11 as read with ICH Q3B, Q3C, Q6A

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 active substance with other active substances (in the case of FDCs), excipients or the container closure system) and process related impurities (e.g. residual solvents in the manufacturing process for the VMP).

Ref: VICH GL39 and VICH GL 11 as read with ICH Q3B, Q3C, Q6A

3.2. P.5.6 Justification of Specifications

The proposed VMP 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 (e.g. degradation products, dissolution method development) 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.

Ref: VICH GL39 and VICH GL 11 as read with ICH Q3B, Q3C, Q6A

3.2. P.6 Reference Standards or Materials

If the same reference standards used for testing the API 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 VMP 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 with suitable specific test for identification (e.g. IR) and analytical procedures should be provided for each primary CCS component. Specifications for film and foil materials should include limits for thickness or area weight. The same should be submitted for the drug delivery devices for multidose solutions, emulsions, suspensions and powders/granules, 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 VMP, aspects that may need justification include choice of the primary packaging materials, protection from light and/or moisture, compatibility with the active substance including sorption to material and leaching and/or any safety aspects of materials of construct, contamination. Primary packaging components are those that are in direct contact with the VMP. 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

3.2. P.8.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include conclusions with respect to storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life. The purpose of stability testing is to provide evidence of how the quality of the VMP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme should also include the study of product-related factors that influence its quality, for example, interaction of API with excipients, container closure systems and packaging materials.

3.2. P.8.1.1 Stress testing

Data on stress testing should be cross-referenced to section 3.2. P.2 "Pharmaceutical Development". If it is not covered in this section, stress testing a single batch of the VMP, in accordance as outlined in section 3.2. S.7.1.1 "Stress testing" should be performed, and the results provided in the dossier. Photostability testing should be conducted on at least one primary batch of the VMP, if not included in the stress stability tests. Additional stress testing of specific types of dosage forms may be appropriate (e.g. cyclic studies for semi-solid products, freeze-thaw studies for liquid products).
Ref: VICH GL5

3.2. P.8.1.2 Accelerated and long-term testing

The applicant should summarize the stability testing program and report the results of stability testing of not less than three (minimum one production scale and two pilot scale) batches of the active substance. The results for each test parameter should be discussed, trends analysed, and a retest date should be proposed.

Stability data should demonstrate stability of the VMP throughout its intended shelf-life. Botswana is under the Climatic Zone IV (a), however with the sole intend purposes to harmonise regional registration requirements, the applicants will be expected to submit stability data generated at Climatic Zone IV (b) stability conditions. Unless otherwise justified, the minimum data required at the time of submitting the dossier (in the general case) should be:

Storage Conditions	Stability data type	Minimum time period
40 ± 2 °C/ 75 ± 5% RH	Accelerated	6 months
30 ± 2 °C/ 65 ± 5% RH	Long-term	12 months

NB: Unless otherwise justified, 40 ± 2°C and 75 ± 5% RH, and 30°C ± 2°C/65± 5%RH are the accelerated and long-term stability condition that will be considered in Botswana.

Extrapolation of data

A VMP is considered stable if it is within the defined specifications when stored at 30 ±2°C / 75 ± 5% RH and 40 ± 2°C / 75 ± 5% RH. The proposed shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data. Information on the analytical procedures used to generate the data and validation of these procedures should be included. Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the dossier, a cross-reference will suffice. If different methodology was used, provide validation of tests for impurities (including degradants), assay and for other tests, as necessary.

For sterile products, sterility should be reported at the beginning and end of shelf life. For parenteral products, subvisible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test interval. Weight loss from plastic containers should be reported over the shelf life.

Any in-use period and associated storage conditions should be justified with experimental data, for example after opening, reconstitution and/or dilution of any sterile and/or multidose products or after first opening of FPPs packed in bulk multidose containers (e.g. bottles of 1000"s). If applicable, the in-use period and storage conditions should be stated in the product information. The information on the stability studies should include details such as storage conditions, strength, batch number, including the API batch number(s) and manufacturer(s), batch size, container closure system including orientation (e.g. erect, inverted, on-side) where applicable; and completed (and proposed) test intervals.

Finished products packaged in semipermeable containers: Aqueous based products packaged in semipermeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. A 5% loss in water from its initial value is considered

a significant change for a VMP packaged in a semipermeable container after three (3) months storage at 40 ± 2°C and NMT 25 ± 5% RH.

For drug substances intended for storage in a refrigerator, at least 6 months accelerated, and 12 months long-term stability data generated at 25°C ± 2°C/60% RH ± 5% RH and 5°C ± 3°C respectively, should be submitted. If significant change occurs between 3- and 6-months' testing at the accelerated storage condition, the proposed re-test period should be based on the real-time data available at the long-term storage condition.

If significant change occurs within the first 3 months' testing at the accelerated storage condition, a discussion should be provided to address the effect of short-term excursions outside the label storage condition, e.g., during shipping or handling. This discussion can be supported, if appropriate, by further testing of a single batch of the drug substance for a period shorter than 3 months but with more frequent testing than usual. It is considered unnecessary to continue to test a drug substance through 6 months when a significant change has occurred within the first 3 months.

For drug substances intended for storage in a freezer, the re-test period should be based on the real-time data obtained at the long-term storage condition. In the absence of an accelerated storage condition for drug substances intended to be stored in a freezer, testing of 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.

Ref: VICH GL3

3.2. P.8.2 Post approval Stability and Commitments

When available long-term stability data on primary batches do not cover the proposed shelf- life granted at the time of assessment of the dossier, a post-approval stability protocol and a commitment should be made to continue the stability studies in order to firmly establish the shelf-life. A written commitment (signed and dated) to continue long-term testing over the shelf-life period should be included in the dossier.

The long-term stability studies for the commitment batches should be conducted through the proposed shelf life on at least three production batches of each strength in each container closure system. Where stability data was not provided for three production batches of each strength, a written commitment (signed and dated) should be included in the dossier.

Ongoing stability programme is established to monitor the product over its shelf life and to determine that the product remains and can be expected to remain within specifications under the storage conditions on the label. Unless otherwise justified, at least one batch per year of product manufactured in every strength and every container closure system, if relevant, should be included in the stability programme (unless none is produced during that year). Bracketing and matrixing may be applicable. A written commitment (signed and dated) to this effect should be included in the dossier.

3.2. P.8.3 Stability data

The actual stability results/reports used to support the proposed shelf life should be provided in the dossier. These stability studies, including forced degradation studies and the stress conditions, should be presented in an appropriate tabular or graphical format. Information on the analytical procedures used to generate the data and validation of these procedures should be included. The impurities should be discussed. The storage conditions and the shelf-life should be defined. All quantitative tests (e.g. individual and total degradation product tests and assay tests), should be reported in actual numerical values rather than vague statements such as "within limits" or "conforms".

Ref: VICH GL3(R), VICH GL4, VICH GL58, VICH GL45, VICH GL5 and VICH GL51 As read with ICH Q1 A (R2)

3.2. R: REGIONAL INFORMATION

3.2. R.1 Batch Production Documents

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

The blank manufacturing documents for each 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:

i. Dispensing, processing, and packaging sections, reflecting all the relevant materials and operational details
ii. Relevant calculations (e.g., for potency adjustment)
iii. Identification of all equipment by type and working capacity
iv. Process parameters (e.g., mixing time, mixing speed, milling screen size, processing temperature range, tablet machine speed, etc.)
v. List of in-process tests (e.g., appearance, pH, potency, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, etc.)
vi. Sampling plan and list of all the steps where sampling should be done (e.g., drying, lubrication, and compression)
vii. The number of samples that should be tested (e.g., blend drawn using a sampling thief from x number of different parts of the blender), and the frequency of testing (e.g., weight variation every x minutes during compression or capsule filling)
viii. All the precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times, etc.)
ix. Theoretical and actual yield; 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. pilot, comparative bioavailability or biowaiver batches, validation, stability or 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 VMP 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: NON-CLINICAL STUDY REPORTS

4.1 Table of contents for the module

4.2.0 Introduction to Non-Clinical Data

Information on this part is required for all veterinary medicinal products containing new active substances. However, for VMPs containing well established ingredients, preclinical data is not required; instead literature review may be submitted. The objective of non-clinical studies is to define the pharmacological actions and toxicological effects of the active substance in test animals and target species, users, consumers and the environment. This normally involves initial studies in laboratory animals and later on pre-clinical studies in the target species, which should take into consideration the following:

- Selection of the relevant animal species
- Age of the animals
- Physiological state of the animals
- The manner of delivery, including dose, route of administration and treatment regimen and the effect on the animals
- Stability of the test medicine under the condition of use
- Safety of personnel.

Preclinical data should be presented in the following sequence:
(a) Objectives
(b) Experimental protocol including methodology and materials
(c) Summarized results and related statistical analysis
(d) Discussions and conclusions
(e) In case of toxicity studies proposed measures to minimize potential toxicity during use of the product

4.2.1 Pharmacological studies

4.2.1.1 Pharmacodynamics

A full description of tests performed to establish the pharmacological actions that are relevant to the proposed indication(s) of the active substance and mechanisms of action should be provided. Where possible it will be helpful to relate the pharmacodynamics of the drug to available data (in terms of selectivity, safety, potency etc.) on other drugs in the same class.

4.2.1.1.1 Other actions (desired/undesired)

An assessment summary of action(s) other than those of therapeutic use should be provided. The results of two or three dosage levels studied should be submitted, with the lowest level representing the ED50 for the active substance's primary action on the animal species being investigated. For drugs, which may be expected to have significant adverse reactions, attempts should be made to estimate the threshold levels.

4.2.1.1.2 Pharmacodynamic interactions

The applicant shall submit data either to establish that such interactions do not occur or that they are clearly recognized and defined. Discuss the pharmacodynamic interactions and mechanisms of interactions of the active substance with other compounds (drug or other substances), which are relevant to proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well elucidated. In case of fixed dose combination or combination packs appropriate data to justify the benefit of combination against single active substance should be given.

4.2.1.2 Pharmacokinetics

Pharmacokinetics studies should be made with single dose by various routes. Repeated dose studies should also be performed when relevant, to establish the pharmacokinetics of chronic drug administration. Metabolic studies should be conducted on species used in toxicological and reproduction studies using the proposed clinical routes of administration.

Where radioactive labelled materials are used in studies, position of label stability and specificity of material should be stated. Where the product contains a combination of drugs, the effect of use of two or more drugs on the pharmacokinetics of one or the other drugs should be established.

Provide studies done to establish the pattern and time course of absorption, distribution, biotransformation, pharmacokinetic interactions and excretion of the active substance and/or its metabolites as described below.

4.2.1.2.1 Absorption

Provide summary of mechanism of absorption, factors affecting absorption, rate and extent of absorption, plasma levels of the active substance and metabolites (peak levels, half-life, etc.). This information should be discussed for different routes. Correlation between plasma drug concentrations and pharmacological effects should be discussed.

4.2.1.2.2 Distribution of active substance and metabolites

Provide a summary and time course of distribution of the active substance and metabolites in body fluids, tissues, and organs. Accumulation, retention of the drug/metabolites in tissues, organs, penetration of blood-brain and placental barriers, plasma binding all these parameters should be reported in quantitative form.

4.2.1.2.3 Biotransformation

Give the pattern and time course of biotransformation of the drug, i.e. sites of metabolism and their importance, metabolic pathway(s), nature and quantities of metabolites, rate of metabolism, pre-systemic metabolites enzyme inhibition or induction, activity of metabolites, if any.

4.2.1.2.4 Pharmacokinetic interactions

Discuss the pharmacokinetic interactions and mechanisms of interactions of the active substance with other compounds (drug or other substances), which are relevant to proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well elucidated.

4.2.1.2.5 Excretion

Summarize the routes and extent of excretion of the drug and its metabolites. State also its excretion in milk in case of lactating animals. Discuss the rate of elimination and factors influencing elimination.

4.2.1.3 Toxicological studies

The scope of toxicological assessment should be described in relation to the proposed clinical use. Information obtained from experimental and biological studies of all aspects of toxicology (general toxicity, acute toxicity studies, subacute toxicity and long-term toxicity studies including teratology, reproduction effects, carcinogenicity, genotoxicity, immunogenicity, microbial affects (e.g. development of resistance), local tolerance (potential for adverse effects at site of administration, etc) is required to establish the safe use of the drug and must be submitted for all new drug applications. The investigation should, if possible, include experiments conducted with the drug in the vehicle intended for therapeutic application or its final pharmaceutical formulation (product).

4.2.1.3.1 General Toxicity Studies

In general toxicity studies, at least three or more routes of administration should be used including one for therapeutic use and at least one other which ensures systemic absorption, i.e. intravenous, intramuscular or subcutaneous. Different dose levels spaced logarithmically should be used. The maximum tolerated dose should be indicated.

All animals dying during the experiment should be autopsied and cause of death determined where possible. Full post-mortem should be carried out on all animals and histopathological studies undertaken on control and dosed groups. Results should be tabulated. Full data for all parameters measured, with mean, range for groups, should be included. If it is expected that the product will be used in young animals, studies should be conducted on both adult and young animals.

4.2.1.3.2 Acute toxicity studies

Principles governing general toxicity studies shall be applicable to acute, subacute and long-term toxicity studies and local tolerability studies LD50 Single-dose toxicity studies can be used to:

(a) Predict the possible effects of acute overdosing in the target species

(b) Predict the possible effects of accidental administration to veterinarians

(c) Predict the doses which may usefully be employed in the repeat dose studies
(d) Assess the relative toxicity of the compound.

Single dose toxicity studies should reveal the acute toxic effects of the substances and the time course for their onset and remission. These studies should normally be carried out in both sexes of at least two mammalian species. One species may be replaced, if appropriate, by an animal species for which the medicinal product is intended. Preferably two different routes of administration should be studied. The route selected should be the same as that proposed for the target species. If substantial exposure of the user of the medicinal product is anticipated, for example for inhalation or dermal contact, these routes should be studied.

4.2.1.3.3 Sub-acute toxicity studies

Repeat dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.
In the case of substances or medicinal products intended solely for use in animals which do not produce food for human consumption, a repeat dose toxicity study in one species of experimental animal will normally be sufficient. This study may be replaced by a study conducted in the target species. The frequency and route of administration, and the duration of the study should be chosen having regard to the proposed conditions of clinical use. The investigator shall give reasons for the extent and duration of the trials and the dosages chosen.
In the case of substances or medicinal products intended for use in food producing animals, the studies should be conducted in at least two species, one of which should be a nonrodent. The investigator shall give reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test substance shall be administered orally. The duration of some of the studies shall be at least 90 days. The investigator shall clearly state and give reasons for the method and frequency of administration and the length of the trials.
The maximum dose should normally be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity. Assessment of the toxic effects shall be based on observation of behaviour, growth, haematology and physiological tests, especially those relating to the excretory organs, and also autopsy reports and accompanying histological data. The choice and range of each group of tests depends on the species of animal used and the state of scientific knowledge at the time.
Ref: VICH GL31 and VICH GL37

4.2.1.3.4 Long term toxicity studies

Where applicable long-term toxicity determinations i.e. one-year chronic study in dogs or a lifetime chronic study in rats, may be required. Long-term animal carcinogenicity studies will usually be required for substances to:
(a) Which veterinary beings will be exposed,
(b) Which have a close chemical analogy with known carcinogens,

(c) Which during mutagenicity testing produced results indicate a possibility of carcinogenic effects
(d) Which gave rise to suspect signs during toxicity testing
The state of scientific knowledge at the time the application is submitted shall be taken into account when designing carcinogenicity studies and evaluating their results.
Ref: VICH GL23

4.2.1.3.4.1 Mutagenicity/Clastogenicity

Mutagenicity tests are intended to assess the potential of substances to cause transmissible changes in the genetic material of cells. If there is any indication of mutagenicity, carcinogenicity studies will be required. Any new substances intended for use in veterinary medicinal products must be assessed for mutagenic properties.
The number and types of tests and the criteria for the assessment of the results shall depend on the state of scientific knowledge when the application is submitted.
Ref: VICH GL28

4.2.1.3.4.2 Reproductive toxicity studies

Reproductive studies will be required if there is any indication of adverse effects on potential reproduction in the preceding preclinical studies. The purpose of such studies is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the medicinal products or substance under investigation.
In the case of substances or medicinal products intended for use in food producing animals, the study of the effects on reproduction shall be carried out in the form of a two-generation study on at least one species, usually a rodent. The substances or product under investigation shall be administered to males and females from an appropriate time prior to mating. Administration should continue until the weaning of the F2 generation. At least three dose levels shall be used. The maximum dose should be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity. Assessment of the effects on reproduction shall be based upon fertility, pregnancy, and maternal behaviour; suckling growth and development of the F1 offspring from conception to maturity and the development of the F2 offspring to weaning.

4.2.1.3.4.3 Study of embryotoxic / fetotoxic effects including teratogenicity

Embryotoxic / fetotoxic, including teratogenicity studies will be required: In the case of substances or medicinal products intended for use in food producing animals, studies of embryotoxic / fetotoxic effects, including teratogenicity, shall be carried out. These studies shall be carried out in at least two mammalian species, usually a rodent and the rabbit. The details of the test (number of animals, doses, time at which administered and criteria for the assessment of results) shall depend on the state of scientific knowledge at the time the application is lodged and the level of statistical significance which the results should attain. The rodent study may be combined with the study of effects on reproductive function. In the case of substances or medicinal products which are not intended for use in food producing animals, to animals which might be used for breeding, a study of embryotoxic/fetotoxic

effects, including teratogenicity, shall be required in at least one species, which may be the target species.

4.2.1.3.4.4 Neurotoxicity

Neurotoxicity studies will be required if there is any indication of such effects in the preceding preclinical studies or if the product is chemically related to a group with such potential.

4.2.1.3.4.5 Immunotoxicity

Where the effects observed during repeated dose studies in animals reveal specific changes in lymphoid organ weights and/or histology and/or changes in the cellularity of lymphoid tissues, bone marrow or peripheral leukocytes, the investigator shall consider the need for additional studies of the effects of the product on the immune system. The state of scientific knowledge at the time the application to be is submitted shall be taken into account when designing such studies and evaluating their results.

Ref: VICH GL22 and VICH GL32

4.3 Field Safety

4.3.1 Target animal species safety

VMPs 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 as follows:

- Injection site safety studies
- Administration site safety studies for dermally applied topical VMPs
- Reproductive safety studies
- Mammary gland safety studies

These studies should be conducted in accordance with the principles of good clinical practice (GCP) or (GLP)

Ref: VICH GL 9 and VICH GL43

4.3.2 User Safety

Accidental exposure of the VMP users has potential risk to cause problems to this population. As such, assessment of the risk presented from the VMP for those handling and administering it, should be performed in accordance with the Guideline on user safety for pharmaceutical veterinary medicinal products EMA/CVMP/543/03-Rev.1 and it should be presented by incorporating the following aspects:

- an appraisal of the inherent toxicity of the VMP
- an appraisal of how and when the user will be exposed to the VMP
- conclusions of the above two aspects resulting in a risk characterization
- proposing how the information will be communicated to the user.

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 should be provided. Studies should cover potential harmful effects to exposure by various routes, e.g. inhalation, topical contact, oral ingestion. The implications to human handling the product should be described and, where appropriate, precautions during preparation and use of the product should be proposed.

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

Exposure to VMP residues can have several harmful effects to people. These include direct toxicity, genotoxicity/carcinogenicity, reproductive toxicity, teratogenicity, allergic reactions and antimicrobial resistance among others. Humans are exposed to these VMP residues through treated animal edible tissues like muscle, liver, kidney, and fat, and treated animal's edible products such as milk, eggs, and honey. Residue study data from pharmacokinetic/tissue residue depletion studies should be provided to justify withdrawal periods for milk, meat, eggs for each species for which the product is indicated. Maximum residue limits in food producing animals should be determined, where no known MRLs exist for a drug substance. All the analytical methods used should be provided. Safety assessment of veterinary drugs residues in food of animal origin should be performed for all new drugs. Relevant pharmacological, toxicological, microbiological end points should be used to establish acceptable daily intake [VICH GL36(R2)]. Pre and post antimicrobial resistance surveillance should be performed on indicator pathogens e.g. E. coli, Salmonella spp.

In summary, these studies should be performed (in accordance with stated guidance document) including pharmacodynamics, pharmacokinetics, chronic oral toxicity (± repeat dose toxicity) [VICH GL31 and VICH GL37], reproductive toxicity [VICH GL22], genotoxicity [VICH GL23(R)], carcinogenicity, [VICH GL28], specific effects (e.g. on gut flora and neurotoxicity), microbiological studies and residue depletion studies in target animals [VICH GL46, VICH GL47, VICH GL48(R), VICH GL49(R), VICH GL 56 and VICH GL57]. The studies should be conducted in accordance with Good Laboratory Practice, using validated analytical methods.

Ref: VICH GL1, VICH GL2, VICH GL32, VICH GL33, VICH GL54

4.3.4 Environmental Safety

VMPs are considered a source of organic and inorganic pollutants that lead to environmental 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 drug and its active metabolites to the environment shall be made taking into account:

(a) The target species, likelihood of exposure, method of excretion of the product and its active metabolites into the environment.

(b) Pattern of use and therefore quantity of drug to be used (herd/flock medication / individual medication)

(c) The method of administration and whether it may lead to direct entry of the product into the environment, e.g. sprays

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

Studies or a review of the published literature 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

Proposed measures to minimize the above potential risks during use of the product shall be described. Data on environmental safety assessment shall be given for the following products:
(a) Antibiotics in poultry, pig and fish feeds
(b) Anthelmintics in large animals e.g. ivermectin
(c) Expired drugs from the market
(d) Effluents from manufacturing plants
(e) Hazardous or potentially hazardous non-pharmaceutical materials (used devices e.g. needles, syringes and gloves)
(e) External preparations
Ref: VICH GL6, VICH GL38 and VICH GL43

Module 5: CLINICAL STUDY REPORTS

Full clinical data should be provided for new VMPs from new APIs. This should include protocols, study reports, and supporting raw data for all studies, such as dose determination, dose confirmation, field efficacy studies in target animal species. These should be performed in accordance with approved international GLP and GCP guidelines; VICH GL9 among other guidance. However, for generic VMPs from well-established pharmaceutical drug substances, VICH GL52 should be followed, and the data presented below should be provided.

5.1 Interchangeability

Applicants for registration of generic product must submit evidence showing that the generic VMP is therapeutically equivalent to its innovator or reference product in the relevant animals by either submitting comparative pharmacodynamic studies or clinical trials.

5.2 Comparative pharmacodynamic studies

Describe the study protocol including the study design, pharmacological or biochemical response measured, measuring instruments used results, statistical methods used and their justification. Tabulation and graphical illustration of results and conclusion.

i. A crossover design is preferred and where it is not appropriate a parallel design is acceptable. The study design must consider the pathology and natural history of the condition.

ii. Studies should be done in healthy subjects or in patients if the disease affects the actions/responses studied.
iii. Inclusion/exclusion criteria must be stated, and non-responders should be identified and excluded prior to begin the study.
iv. Measured pharmacological response should be relevant to the claimed therapeutic uses where there are more than one therapeutic use studies should be done to demonstrate the therapeutic equivalence for each use.
v. Measurement of responses should as far as possible be quantitative, measured under double blind conditions and be recorded in an instrument producer/instrument recorded fashion. The methodology must be validated for precision, accuracy, reproducibility and specificity.
vi. The principles of Good Veterinary Clinical Practice (GVCP) and Good Laboratory Practice (GLP) should be adhered to during the study.
vii. Where possible the effect can be graphically illustrated using the area under the effect time curve, maximum effect and time of maximum effect.

In using pharmacodynamic methods, the following requirements must be satisfied:

- The response can be measured precisely over a reasonable range
- The response can be measured repeatedly to obtain time course from the beginning to end of the response
- It should be possible to derive the common parameters of comparison.
- It should be possible to derive the common parameters of comparison like Cmax, Tmax and AUC.

The test and reference product should not produce a maximal response during the course of study.

5.3 Comparative clinical data

Describe in detail the study protocol, which should, include the title of the study investigator(s), location, justification and objective, dates, time, duration, observation periods and justification thereof, study design (randomization methods description of design e.g. crossover or parallel etc), inclusion, exclusion, criteria, methods and treatments, specification of comparator and placebo, results (definition of ethical endpoints measured, methods, measured and recording clinical response (scoring system for endpoints). Statistical methods used and their justification.

i. Comparative clinical studies are required in cases where pharmacodynamic studies cannot be done i.e. when plasma concentration time profile data is not suitable to assess therapeutic equivalence or lack of meaningful pharmacodynamic parameters which, are measured (quantified).
ii. The number of animals chosen, and acceptance limits should be justified.

Ref: VICH GL9, VICH GL52 and EMA/CVMP/016/2000-Rev.3-corr

ANNEX I: APPLICATION FORM

ANNEX II: QUALITY INFORMATION SUMMARY (QIS)

ANNEX III: QUALITY OVERALL SUMMARY (QOS)

ANNEX IV: BIOEQUIVALENCE TRIAL INFORMATION FORM

ANNEX V: BIOWAIVER APPLICATION FORM – BCS based

ANNEX VI: BIOWAIVER APPLICATION FORM – Additional Strength

ANNEX VII: PHARMACEUTICAL VMPs SCREENING CHECKLIST