RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR REGISTRATION OF VETERINARY PHARMACEUTICAL PRODUCTS

AUGUST, 2025

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FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by the Law N° 003/2018 of 09/02/2018. One of the functions of Rwanda FDA is to regulate matters related to quality, safety, and efficacy of Veterinary pharmaceutical products to protect public health by increasing access and availability of essential medicines.

In consideration of the provisions of the technical regulations N°. DFAR/HMDAR/TRG/001 Rev_3 of 28th September 2022 governing the registration of medicinal products. Rwanda FDA has issued revised "*Guidelines No: DD/VMDR/GDL/001 Version 2 for registration of veterinary pharmaceutical products."*

These Guidelines have therefore been reviewed in order to cope with the new developments in line with the requirements for marketing authorisation. They provide guidance on the content and format of information to be presented in registration dossiers submitted to Rwanda FDA for registration of veterinary pharmaceutical products in Rwanda.

Adherence to the guidelines by the manufacturers/applicants will facilitate timely assessments and approvals of pharmaceutical product application dossiers for marketing authorization. Rwanda FDA acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines.

Prof. Emile BIENVENU
Director General

Digitally signed by RWANDA FDA(Director General)
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22/07/2025	2	(a) Change of the document title to make it clearer and concise (b) Adoption of the new guidelines template according to the updated SOP on document control (c) Change of mode of application submission (d) Update of the registration certificate content and format (e) Update of the application processing timeline (f) Update of the current regulation governing tariff fees and charges on services (g) Update of the current regulation governing Medicinal products (h) Editorial changes

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ACRONYMS AND ABBREVIATIONS

VPP	Veterinary Pharmaceutical Product
LOD	Loss on Drying
NCE	New Chemical Entity
NMT	Not More Than
PhEur	European Pharmacopoeia
QA	Quality Assurance
RH	Relative Humidity
TSE	Transmissible Spongiform Encephalopathy
VICH	Veterinary International Conference on Harmonization requirements for Registration of Veterinary pharmaceutical products

GLOSSARY / DEFINITIONS

The definitions provided below apply to the words and phrases used in these guidelines. The following definitions are provided to facilitate interpretation of the guidelines.

"Applicant" means a person who applies for registration of a medicinal product to Rwanda FDA, who must be the owner of the product. He may be a manufacturer or a person to whose order and specifications, the product is manufactured. After the product is registered, the applicant shall be the "Marketing Authorisation Holder".

"Approve" or "approval" means official consent by the Authority as an acceptance of a pharmaceutical product or practices related to that pharmaceutical product to be available on the market in Rwanda.

"Authority" means the Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established under the article 2 of the Law No. 003/2018 of 09/02/2018.

"Certificate of registration" means a certificate issued by the Authority after its approval to market and sell a product in Country.

"Good Manufacturing Practice" means Practices prescribed by the Authority for the manufacturing of products to ensure that such products are of good quality, safe and effective for intended use.

"Label" means any tag, brand, mark, pictorial or other descriptive matter, written, printed stencilled, marked, embossed or impressed on or attached to a container of any medicinal product.

"Local Technical Representative": Means any registered company in Rwanda and licensed by Rwanda FDA to deal with regulated products that has received a mandate from the Applicant to act on his/her behalf with regard to matters pertaining to the registration of regulated products.

"Manufacture" means all operations of receipt of materials, production, packaging, repackaging, labelling, relabelling, quality control release, storage, and distribution of Active Pharmaceutical Ingredients (APIs) and related controls.

"Manufacturer" means a company that carries out operations such as production, packaging, repackaging, labelling and relabelling of products regulated, by Rwanda FDA.

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

"Medicinal product" means any medicine or similar product, which is subject to control under health legislation in the manufacturing or importing State.

Includes human and veterinary drugs; human and animal vaccines and other biological products, poisonous substances, herbal medicines, medicated cosmetics, laboratory and household chemicals and pesticides.

"Pharmaceutical product" Any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct or carry out modification of organic or mental functions. It also means products used in disinfecting premises in which food and drugs are manufactured, prepared or stored, cleaning hospitals, equipment and farm houses.

CHAPTER ONE: INTRODUCTION

I.1 Background

In pursuance of Law Nº 003/2018 of 09/02/2018 establishing Rwanda Food and Drugs Authority, determining its mission, organization, and functioning, especially in article 9; Considering the provisions of the technical regulation No DFAR/HMDAR/TRG/001 Rev_3 of 28th September 2022 governing the registration of medicinal products. The authority has issued revised "*Guidelines No DD/VMDR/GDL/001 Ver_2 for registration of veterinary pharmaceutical products".*

The present guidelines have therefore been reviewed in order to cope with the new developments in line with the requirements for marketing authorisation. The reviewed guidelines entitled "*Guidelines No DD/VMDR/GDL/001 Ver_2 for registration of veterinary pharmaceutical products* provide guidance on the content and format of information to be presented in registration dossiers submitted to Rwanda FDA for registration of veterinary pharmaceutical products in Rwanda.

These guidelines present a common Technical Document (CTD) format for the preparation of an application that will be submitted to the Authority for registration of veterinary pharmaceutical products. This document provides conditions under which a veterinary pharmaceutical product shall be approved and registered in Rwanda.

According to the CTD format, the guidelines set out procedures and requirements for the implementation of Veterinary Pharmaceutical Products Registration and they are arranged as follows:

Module 1: Administrative Requirements;
Module 2: Overviews and summaries;
Module 3: The Quality Requirements for the Active Pharmaceutical Ingredients (API) and Finished Pharmaceutical Products (FPP);
Module 4: Non-Clinical study report;
Module 5: Clinical study report.

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

I.2 Scope

These guidelines provide guidance to the applicants intending to register Veterinary pharmaceutical products in Rwanda. It also assists the Authority during the full assessment and registration of VPPs.

I.3 Preparation and presentation of information in CTD format

The applicant shall prepare and present the product dossier information in CTD format according to the requirements as stipulated in these guidelines: The application should be typed in **English**, **Kinyarwanda and French**.

The application must contain a complete index to the various appendices. The summaries (Quality Information Summary, Quality Overall Summary, Bioequivalence Trial Information and Biowaiver Application Form) should be formatted as word document downloadable on Authority's website and the body data in PDF.

All pages of the application should be numbered in the style: *page x of y*. Payment of fees shall be made in accordance to regulation Nº: ODDG/RES/TRG/001 Governing Tariff/Fees and Charges on Services Rendered by Rwanda Food and Drugs Authority. The fees are for each respective product registration excluding transfer and other charges.

The application shall be submitted to Rwanda FDA via Integrated Regulatory Information Management System (iRIMS).

The PDF documents should be in Optical Character Recognition, selectable and searchable.
A separate application is required for each product. The following products will be regarded as either being the same product or separate product applications.

#	TYPE OF FORMULATION AND APPLICATION	APPLICATION	
		Same	**Separate**
1	**Each individual dosage form of a particular medicine**		**X**
2	**Variations of the active pharmaceutical ingredient (API) of a Product**		**X**
3	**Tablets/Capsules/Suppositories/Lozenges**		
	(a) Different pack-sizes of exactly the same strength and formulation.	**X**	
	(b) Different strengths and formulations.		**X**
	(c) Uncoated and coated tablets of the same strength and formulation		**X**
4	**Syrups/Liquids/Solutions (excluding parenterals)/ Creams/Ointments.**		
	(a) Different container sizes of the same strength and formulation	**X**	
	(b) The same container size of different strengths and formulations.		**X**
5	**Ampoules and Vials and Large Volume Parenterals**		**X**
	Ampoules or single dose vials containing identical solutions of the same strength but of different volumes (i.e. resulting in different total doses).		**X**
	(a) Ampoules containing solutions of different strengths.		**X**

	(b) Ampoules and single dose vials containing e.g. dry powder, crystals of different mass		**X**
	(c) Ampoules and single dose vials containing the same respective masses of e.g. dry powder, crystals.	**X**	
	(d) Ampoules, single dose vials, as well as pre-filled disposable syringes and cartridges containing identical solutions of the same strength and same volume of liquid.	**X**	
	(e) Ampoules containing "water for injection", but of different volumes. Special ampoules of dry powder and "water for injections" contained in the same unit, but intended for mixing at the time of injection if water for injections is fully described in dossier.	**X**	
	(f)Ampoules containing identical solutions of different volumes used only as diluents in the reconstitution of a preparation for parenteral use.	**X**	
	(g) Multidose vials containing different volumes of the same strength and formulation with the same dosage schedule.	**X**	
	(h) Multidose vials and a single dose ampoule or vial of the same formulation if the single-dose ampoule or vial corresponds to the dose indicated for the Multidose vial.	**X**	
	(i)Multidose vials containing dry powder of different mass of the reconstituted.	**X**	
	(j)An ampoule of diluents packed together with any preparation including biological medicines if diluent is fully described in dossier.	**X**	
	(k) Infusion solutions of the different volumes and of the same formulation which are packed in	**X**	

	containers of exactly the same type of material depending on the relevant information submitted.		
	(l) Infusion solutions of the different volumes and of the same type of material depending on the relevant information submitted.	**X**	
	(m) Solutions of the same formulation and of the same or different volume which are packed in containers made of different types of materials.	**X**	
	(n) A preparation, packed in plastic containers, intended to be marketed in glass containers containing the same volume and the same formulation.	**X**	
	(o) Products with the same strength and formulation but with different colours and/or flavours.		**X**
	(p) Applications containing the same API(s) applying for additional indications which render the product in a different scheduling status, or different pharmacological classification, or have any other restrictions imposed other than the original application.		**X**
	(q) Removal of antimicrobial preservative from single dose presentation of registered vaccine that included a preservative in the original approved formulation		**X**
6.	**Same formulation with different proprietary names whether of the same or different applicants**		**X**

I.4 Officially recognized references

The official recognized pharmacopoeias by the Authority are British Pharmacopoeia (BP), European Pharmacopoeia (Ph.Eur.), The International Pharmacopoeia (Ph.Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP). References should be cited in accordance with the current edition of compendia.

When reference is made to specifications, quality control procedures and test methods in official recognized compendia or scientific publications, full references and copies of relevant pages

shall be enclosed. All in-house processes quoted in the documentation must have been validated and appropriate references cited.

I.5 Submission of application

All applications for product registration for either locally manufactured or imported shall be submitted via online portal iRIMS available on Rwanda FDA website https://www.irims.rwandafda.gov.rw/portal. If the applicant is a foreign company, the applicant shall appoint a local technical representative.

I.6 Rwanda FDA Dossier Assessment Procedures

After receiving the VPP registration application, Rwanda FDA shall proceed with screening of the dossier for completeness. In the event that the dossier is incomplete, it will not be scheduled for assessment and the applicant will be notified within 30 working days and requested to comply with requirements in writing.

A product dossier is assessed by two assessors to provide scientific and regulatory oversight regarding the quality, safety and efficacy of the product under assessment. There might be cases where the application dossier deems necessary to be assessed by more than two assessors for full assessment.

The Authority reserves the right to request any additional information to the applicant for establishing the quality, safety and efficacy of veterinary pharmaceutical products in Rwanda.

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

In the event that the responses to the queries are not submitted within ninety (90) working days from the date they were issued, it will be considered that the applicant has withdrawn the application unless the applicant has requested for extension of deadline. Thereafter, registration of the VPP may only be considered upon submission of a new application.

I.7 Compliance to the Good Manufacturing Practices (GMP)

The GMP inspection is part of the VPP registration process. Rwanda FDA should conduct inspection of the facility or use other means to verify whether the manufacturing site complies with GMP requirements and/or guidelines before a product is registered.

No product shall be registered unless the facility complies with GMP requirements. During the assessment, assessors may highlight GMPs issues and communicate to the division that has mandate of inspection and compliance.

More information on GMP requirements and applications for GMP inspection is detailed in the Rwanda FDA Guidelines on Good Manufacturing Practices and their annexes downloadable from Authority's website.

I.8 Rwanda FDA Peer Review Committee for VPP Registration

After the completion of the Dossier Assessment, a final assessment report shall be presented to the Internal Technical Committee for review and recommendation for marketing authorization approval or rejection. In the event, that there is safety, quality or efficacy issues to be resolved as per the decision of the Internal Scientific Review Committee, the application shall remain pending until the resolution of the raised issues.

Rwanda FDA will register the product in the event that data on safety, quality and efficacy is considered satisfactory and a registration certificate will be granted. The registration shall be valid for a period of five (5) years. In the event that Rwanda FDA suspends or cancels the registration, a written official communication shall be made to the applicant.

I.9 Timelines for VPPs Registration

Product dossiers shall be scheduled for assessment according to the First in First out (FIFO) basis upon compliance of the requirements. A new application shall be processed within twelve (12) months of receipt of the application.

The applicant will be required to provide any requested additional data within ninety (90) working days. Additional data or query responses shall be processed within sixty (60) working days.

Figure 1. Graphical illustration of timeline

CHAPTER II: ORGANIZATION OF THE COMMON TECHNICAL DOCUMENT (CTD)

MODULE 1: ADMINISTRATIVE AND PRESCRIBING INFORMATION

Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondence and annexes (drug residue assessments and/or antibiotic resistance evaluation reports), as needed.
Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes. Documents should be organized in the order listed below:

1.1. Comprehensive Table of Contents for all Modules

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

1.2. Cover letter

A cover letter (**Annex I**) should be submitted in the product dossier and placed at the beginning of Module 1. The cover letter for product registration shall be dated and signed by the applicant. The format is downloadable from Rwanda FDA website.

1.3. Manufacturing and Marketing Authorization

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

1.4. Application Information

1.4.1. Language

All applications and supporting documents shall be in English

1.4.2. Application form

An application to register a pharmaceutical product for veterinary use must be accompanied by a completed Application Form (Annex II) downloadable from Rwanda FDA website. The application form should be dully filled with relevant information and attachments, dated signed and stamped appropriately.

If the applicant is not the manufacturer of the product, a duly signed and dated manufacturing agreement between the applicant and the actual manufacturer must be submitted. This agreement should clearly outline the roles and responsibilities of each party.

1.4.3. Data Presentation

Generally, data to be presented in the application for registration of Veterinary Pharmaceutical Product should be compiled in accordance with the specified summarised table below:

Required modules for each type of medicinal product

	Product type	Required modules				
		I	II	III	IV	V
		SmPC	**API**	**FPP**	Pre-clinical Pharmacotoxicological	Clinical Safety and Efficacy
1	Innovator	√	√	√	√	√
2	Innovator fixed-dose combination	√	√	√	√	√
3	Innovator variants: either as single or composite variation in dosage level, form, route of administration, or indication.	√	√	√	Bridging studies data	Bridging studies data
4	Single active ingredient or Fixed dose combination generic.	√	√	√	X	X

Key: SPC Summary of Product Characteristics
API Active Pharmaceutical Ingredient
FPP Finished Pharmaceutical Product
TE Therapeutic Equivalence Data
√ Required
X Not required

For generic medicines data on quality and therapeutic equivalence in target animals shall be presented in separate files.

1.5. Product Information and Labelling

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

1.5.1. Prescribing information (Summary of Product Characteristics)

All prescription medicines should be accompanied by SmPC. The Prescribing information is not a promotional document. Statements of a promotional nature such as “x is the safest drug” are not acceptable.
An applicant shall prepare and present prescribing information in the contents and format as provided in annex XI.

1.5.2. Container labelling

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

1.5.3. Information Leaflet

Every container of a veterinary pharmaceutical product shall be accompanied with information leaflet. Provide two copies of information on A4 paper and also specimens as they will appear with the commercial product. The contents and format of the leaflet are as provided in annex X of this guideline.

1.5.4. Mock-ups and specimens

The applicant should include mock-ups of the commercial sample.

1.6. Good Manufacturing Practice

For all medicines, irrespective of the country of origin, all key manufacturing and/or processing steps in the production of active pharmaceutical ingredient ingredients and finished veterinary pharmaceutical products must be performed in plants that comply with Rwanda FDA GMP guidelines. Attach a WHO type certificate of GMP. For more information on GMP requirements and application for GMP inspection, refer Rwanda FDA Guidelines on Good Manufacturing Practice for more guidance.

1.7. Product samples

Two commercial samples of each pack size shall be submitted to Rwanda FDA Head Office. Those samples should be accompanied by a cover letter (Annex I) and a printed notification email clearly stating the application reference number generated by the Rwanda FDA portal at the time of submission.

Batch number, Manufacturing Date and Expiry Date should be dynamically printed on packages for all veterinary pharmaceutical product in Rwanda except in situations where there is space restriction; the details can be on secondary packages with the primary pack having at least the batch number and expiry date. Pre-printing of the batch number, manufacturing date and Expiry Date will not be acceptable.

1.8. Certificates of Suitability to the CEP or APIMF

An application to register a new veterinary pharmaceutical product (or vary an existing product) may make reference to an Active Pharmaceutical Master File (APIMF) or certificate of suitability to the monographs of the European Pharmacopoeia (CEP).

Where reference is made to an APIMF, the FPP applicant must have written permission to access the APIMF from the APIMF holder and must provide the APIMF file number to Rwanda FDA.

Where reference is made to a CEP, the finished product applicant must have written permission from the API manufacturer to access the CEP and must provide a copy of the CEP, and any appendices, to Rwanda FDA.

Complete copies of the CEP (including any annexes) should be provided in Module 1. The applicant should provide the Letter of Access to CEP or Letter of Access to APIMF, as appropriate from API manufacturer according to the formats for Letters of Access to CEP and APIMF (refer to the Annex V and VI), and these letters should be included in Module 1.

The applicant's (open) part of the APIMF should be included in Module 3.2.S of the Quality documentation presented in the CTD-format. The API manufacturer's restricted (closed) part is supplied to Rwanda FDA directly by the API manufacturer when required.

MODULE 2: OVERVIEWS & SUMMARIES

2.1. Table of contents of Module 2

A table of content of module 2 should be provided.

2.2. CTD Introduction

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). This section should be a 2-3-page summary of the entire application.

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.
The QOS should include sufficient information from each section to provide the quality assessor 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. The QOS should include 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), including cross-referencing to volume and page number in other Modules.

The quality overall summary – product dossiers (QOS-PD) template (*refer to the Annex III)* should be completed for veterinary pharmaceutical products containing APIs of synthetic or semi synthetic origin and their corresponding FPPs. The QOS should be provided in both word and PDF version. The word version is a must. All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by reporting "not applicable" in the appropriate area with an accompanying explanatory note.
The use of tables to summarize the information is encouraged, where possible.

The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths), as necessary. These tables are included as illustrative examples of how to summarize information. Other approaches to summarize information can be used if they fulfil the same purpose.

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

Information from 3.2.S.2 should be included as follows:

(a) A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality;
(b) A flow diagram, as provided in 3.2.S.2.2;
(c) A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the drug substance, as described in 3.2.S.2.3;
(d) A discussion of the selection and justification of critical manufacturing steps, process controls, and acceptance criteria. Highlight critical process intermediates, as described in 3.2.S.2.4;
(e) A description of process validation and/or evaluation, as described in 3.2. S.2.5;
(f) 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. 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 Module 4 and 5 of the dossier.

2.3. S.3. Characterisation

For New Chemical entities (NCE):
A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included. When a drug substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the nonclinical and clinical studies, and information should be given as to the stereoisomer of the drug substance that is to be used in the final product intended for marketing.

For NCE, The QOS should summarise the data on potential and actual impurities arising from the synthesis, manufacture and/or degradation, and should summarise the basis for setting the acceptance criteria for individual and total impurities. The QOS should also summarise the impurity levels in batches of the drug substance used in the non-clinical studies, in the clinical trials, and in typical batches manufactured by the proposed commercial process. The QOS should state how the proposed impurity limits are qualified.

A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate should be included.

2.3. S.4. Control of Drug Substance

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included. Specification from 3.2.S.4.1 should be provided. A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

2.3. S.5. Reference Standards or Materials

Information from 3.2.S.5 (tabulated presentation, where appropriate) should be included.

2.3. S.6. Container Closure System

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

2.3. S.7. Stability

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf life. Where relevant, as described in 3.2. S.7.1.
The post-approval stability protocol, as described in 3.2.S.7.2, should be included. A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3. P. Finished Pharmaceutical Product (FPP)

2.3. P.1. Description and Composition of the FPP

Information from 3.2.P.1 should be provided.
Composition from 3.2.P.1 should be provided.

2.3. P.2. Pharmaceutical Development

A discussion of the information and data from 3.2.P.2 should be presented. A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3. P.3. Manufacture

Information from 3.2.P.3 should include:

(a) Information on the manufacturer;
(b) 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;
(c) A flow diagram, as provided under 3.2. P.3.3;

(d) 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

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

2.3. P.5. Control of FPP

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterization of impurities should be provided. Specification(s) from 3.2.P.5.1 should be provided.
A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

2.3. P.6. Reference Standards or Materials

Information from 3.2.5.6 (tabulated presentation, where appropriate) should be included.

2.3. P.7. Container Closure System

A brief description and discussion of the information in 3.2.P.7 should be included.

2.3. P.8. Stability

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusion with respect to storage conditions and shelf life and, if applicable, in use storage conditions and shelf life should be given.
A tabulated summary of the stability results from 3.2.P.8.3 should be included.
The post-approval stability protocol, as described in 3.2.2.8.2, should be provided.

2.4. Overview and Summary of Non Clinical and Clinical Documentation

General Principles of Nonclinical Overview and Summaries

The primary purpose of the Nonclinical Written and Tabulated Summaries should be to provide a comprehensive factual synopsis of the nonclinical data. The interpretation of the data, the clinical relevance of the findings, cross-linking with the quality aspects of the pharmaceutical, and the implications of the nonclinical findings for the safe use of the pharmaceutical (i.e., as applicable to labelling) should be addressed in the Overview.

2.4.1 NEW CHEMICAL ENTITIES ONLY

2.4.1.1. Nonclinical Overview

The Nonclinical Overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Nonclinical Overview should not exceed

about 30 pages.

The Nonclinical Overview should contain appropriate reference citations to the Tabulated Summaries.

2.4.1.1.1 Content and Structural Format

The Nonclinical Overview should be presented in the following sequence:

(a) Overview of the nonclinical testing strategy;
(b) Pharmacology;
(c) Pharmacokinetics;
(d) Toxicology;
(e) Integrated overview and conclusions;
(f) List of literatures references.

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in physiology, anti-product antibodies, and cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed.

Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (Area under the plasma concentration time curve (AUC), Maximum plasma concentration (Cmax) and other appropriate parameters) should be discussed and the limitations and utility of the nonclinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose-dependency and degree of reversibility (or irreversibility), and species related differences should be evaluated and important features discussed, particularly with regard to:

(a) Pharmacodynamics;
(b) Toxic signs;
(c) Causes of death;
(d) Pathologic findings;
(e) Genotoxic activity - the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds;
(f) Carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data;
(g) The carcinogenic risk to humans - if epidemiologic data are available, they should be taken into account;
(h) Fertility, embryofetal development, pre-and post-natal toxicity;

(i) Studies in juvenile animals;
(j) The consequences of use before and during pregnancy, during lactation, and during neonatal development;
(k) Local tolerance;
(l) Other toxicity studies/ studies to clarify special problems.

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect / phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

(a) Animal species used;
(b) Numbers of animals used;
(c) Routes of administration employed;
(d) Dosages used;
(e) Duration of treatment or of the study.

If alternatives to whole-animal experiments are employed, their scientific validity should be discussed. The Integrated Overview and Conclusions should clearly define the characteristics of the pharmaceutical product as demonstrated by the nonclinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use.
Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the nonclinical findings for the safe animal use of the pharmaceutical should be discussed (i.e., as applicable to labelling).

2.4.1.2 NONCLINICAL WRITTEN AND TABULATED SUMMARIES

2.4.1.2.1 Nonclinical Written Summaries

2.4.1.2.1.1 Introduction

This guideline is intended to assist authors in the preparation of nonclinical pharmacology, pharmacokinetics, and toxicology written summaries in an acceptable format.
This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.
The sequence and content of the Nonclinical Written Summary sections should cover the following key elements:
Brief information concerning the pharmaceutical's structure (preferably, a structure diagram should be provided) and pharmacologic properties.
Information concerning the pharmaceutical's proposed clinical indication, dose, and duration of use.

However, no guideline can cover all eventualities, hence common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. i.e. applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.
Whenever appropriate, age- and species-related effects should be discussed.

Relevant findings with stereoisomers and/or metabolites should be included, as appropriate. Consistent use of units throughout the Summaries will facilitate their review. A table for converting units might also be useful.
In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure at any species given the maximum intended doses.

General Presentation Issues
Order of Presentation of Information within Sections:
When available, in vitro studies should precede in vivo studies.
Where multiple studies of the same type need to be summarised within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).

Species should be ordered as follows:

(a) Mouse;
(b) Rat;
(c) Hamster;
(d) Other rodent;
(e) Rabbit;
(f) Dog;
(g) Non-human primate;
(h) Other non-rodent mammal.

Routes of administration should be ordered as follows:

(a) Oral;
(c) Intravenous;
(d) Intramuscular;
(e) Intraperitoneal;
(f)Subcutaneous;
(g) Inhalation;
(h) Topical;
(i)Other.

Use of Tables and Figures

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures.
To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries. Throughout the text, reference citations to the Tabulated Summaries should be included, in the following format: (Table X.X, Study/Report Number).

Length of Nonclinical Written Summaries Although there is no formal limit to the length of the Nonclinical Written Summaries, it is recommended that the total length of the three Nonclinical Written Summaries in general not exceed 100-150 pages.

Sequence of Written Summaries and Tabulated Summaries.

The following order is recommended:

(a) Introduction;
(b) Written Summary of Pharmacology;
(c) Tabulated Summary of Pharmacology;
(d) Written Summary of Pharmacokinetics;
(e) Tabulated Summary of Pharmacokinetics;
(f) Written Summary of Toxicology;
(g) Tabulated Summary of Toxicology.

2.4.1.2.1.2 Pharmacology Written Summary

Within the Pharmacology Written Summary, the data should be presented in the following sequence:

(a) Brief Summary;
(b) Primary Pharmacodynamics;
(c) Secondary Pharmacodynamics;
(d) Safety Pharmacology;
(e) Pharmacodynamic Drug Interactions;
(f)Discussion and Conclusions;
(g) Tables and Figures (either here or included in text).

2.4.1.2.1.2.1 Brief Summary

The principal findings from the pharmacology studies should be briefly summarized in approximately 2 to 3 pages.

This section should begin with a brief description of the content of the pharmacologic data package, pointing out any notable aspects such as the inclusion/exclusion of particular data (e.g., lack of an animal model).

2.4.1.2.1.2.2 Primary Pharmacodynamics

Studies on primary pharmacodynamics should be summarised and evaluated. Where possible, it would be helpful to relate the pharmacology of the drug to available data (in terms of selectivity, safety, potency, etc.) on other drugs in the class.

2.4.1.2.1.2.3 Secondary Pharmacodynamics

Studies on secondary pharmacodynamics should be summarised by organ system, where appropriate, and evaluated in this section.

2.4.1.2.1.2.4 Safety Pharmacology

Safety pharmacology studies should be summarised and evaluated in this section. In some cases, secondary pharmacodynamic studies can contribute to the safety evaluation when they predict or assess potential adverse effect(s) in animals. In such cases, these secondary pharmacodynamic studies should be considered along with safety pharmacology studies.

2.4.1.2.1.2.5 Pharmacodynamic Drug Interactions

If they have been performed, pharmacodynamic drug interaction studies should be briefly summarised in this section.

2.4.1.2.1.2.6 Discussion and Conclusions

This section provides an opportunity to discuss the pharmacologic evaluation and to consider the significance of any issues that arise.

2.4.1.2.1.2.7 Tables and Figures

Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

2.4.1.2.1.3 Pharmacology Tabulated Summary

2.4.1.2.1.3.1 Pharmacokinetics Written Summary

The sequence of the Pharmacokinetics Written Summary should be as follows:

(a) Brief Summary;
(b) Methods of Analysis;
(c) Absorption;
(d) Distribution;
(e) Metabolism;
(f) Excretion;
(g) Pharmacokinetic Drug Interactions;
(h) Other Pharmacokinetic Studies;
(i) Discussion and Conclusions;
(j) Tables and Figures (either here or included in text).

2.4.1.2.1.3.1.1 Brief Summary

The principal findings from the pharmacokinetics studies should be briefly summarized in approximately 2 to 3 pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasising, for example, whether the species and strains examined were those used in the pharmacology and toxicology evaluations, and whether the formulations used were similar or identical.

2.4.1.2.1.3.1.2 Methods of Analysis

This section should contain a brief summary of the methods of analysis for biological samples, including the detection and quantification limits of an analytical procedure.

If possible, validation data for the analytical method and stability of biological samples should be discussed in this section. The potential impact of different methods of analysis on the interpretation of the results should be discussed in the following relevant sections.

2.4.1.2.1.3.1.3. Absorption

The following data should be summarised in this section:

2.4.1.2.1.3.1.4. Distribution

The following data should be summarised in this section:

Tissue distribution studies

Protein binding and distribution in blood cells
Placental transfer studies

2.4.1.2.1.3.1.5. Metabolism (interspecies comparison)
The following data should be summarised in this section:
Chemical structures and quantities of metabolites in biological samples
Possible metabolic pathways
Pre-systemic metabolism (GI/hepatic first-pass effects)
In vitro metabolism including P450 studies
Enzyme induction and inhibition

2.4.1.2.1.3.1.6. Excretion
The following data should be summarised in this section:
Routes and extent of excretion
Excretion in milk

2.4.1.2.1.3.1.7. Pharmacokinetic Drug Interactions
If they have been performed, nonclinical pharmacokinetic drug-interaction studies (in vitro and/or in vivo) should be briefly summarised in this section.

2.4.1.2.1.3.1.8. Other Pharmacokinetic Studies
If studies have been performed in nonclinical models of disease (e.g., renally impaired animals), they should be summarised in this section.

2.4.1.2.1.3.1.9. Discussion and Conclusions
This section provides an opportunity to discuss the pharmacokinetic evaluation and to consider the significance of any issues that arise

2.4.1.2.1.3.1.9. Tables and Figures
Text tables and figures can be included at appropriate points throughout the summary within the text.

Alternatively, there is the option of including tables and figures at the end of the summary.

2.4.1.2.1.4 Pharmacokinetics Tabulated Summary

2.4.1.2.1.4.1 Toxicology Written Summary

The sequence of the Toxicology Written Summary should be as follows:

(a) Brief Summary;
(b) Single-Dose Toxicity;
(c) Repeat-Dose Toxicity;
(d) Genotoxicity;
(e) Carcinogenicity;
(f) Reproductive and Developmental Toxicity;
(g) Studies in Juvenile Animals;
(h) Local Tolerance;
(i) Other Toxicity Studies;
(j) Discussion and Conclusions;

(k) Tables and Figures (either here or included in text).

2.4.1.2.1.4.1 .1. Brief Summary

The principal findings from the toxicology studies should be briefly summarized in a few pages (generally not more than 6). In this section, the extent of the toxicological evaluation can be indicated by the use of a table listing the principal toxicological studies (results should not be presented in this table).

2.4.1.2.1.4.1.2. Single-Dose Toxicity

The single-dose data should be very briefly summarised, in order by species, by route. In some instances, it may be helpful to provide the data in the form of a table.

2.4.1.2.1.4.1.3. Repeat-Dose Toxicity (including supportive toxicokinetics evaluation) Studies should be summarised in order by species, by route, and by duration, giving brief details of the methodology and highlighting important findings (e.g., nature and severity of target organ toxicity, dose (exposure)/ response relationships, no observed adverse effect levels, etc.

2.4.1.2.1.4.1 .4. Genotoxicity

Studies should be briefly summarised in the following order:

(a) in vitro non-mammalian cell system;
(b) in vitro mammalian cell system;
(c) in vivo mammalian system (including supportive toxicokinetics evaluation);
(d) Other systems.

2.4.1.2.1.4.1 .5. Carcinogenicity (including supportive toxicokinetics evaluations)

A brief rationale should explain why the studies were chosen and the basis for high-dose selection.

Individual studies should be summarised in the following order:

Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics);

Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics);

Other studies.

2.4.1.2.1.4.1 .6. Reproductive and Developmental Toxicity

Studies should be summarised in the following order, giving brief details of the methodology and highlighting important findings:

Fertility and early embryonic development

(a) Embryo-fetal development;
(b) Prenatal and postnatal development, including maternal function;
(c) Studies in which the offspring (juvenile animals) are dosed and/or further evaluated, if such studies have been conducted. If modified study designs are used, the sub-headings should be modified accordingly.

2.4.1.2.1.4.1 .7. Local Tolerance

If local tolerance studies have been performed, they should be summarised in order by species,

by route, and by duration, giving brief details of the methodology and highlighting important findings.

2.4.1.2.1.4.1 .8. Other Toxicity Studies (if available)
If other studies have been performed, they should be summarised. When appropriate, the rationale for conducting the following studies should be provided:

(a) Antigenicity;
(b) Immunotoxicity;
(c) Mechanistic studies (if not reported elsewhere);
(d) Dependence;
(e) Studies on metabolites;
(f) Studies on impurities;
(g) Other studies.

2.4.1.2.1.4.1.9. Discussion and Conclusions
This section should provide an opportunity to discuss the toxicological evaluation and the significance of any issues that arise. Tables or figures summarizing this information are recommended.

2.4.1.2.1.4.1 .10. Tables and Figures
Text tables and figures can be included at appropriate points throughout the summary within the text. Alternatively, tables and figures can be included at the end of the summary.

(a) Toxicology Tabulated Summary;
(b) Nonclinical Tabulated Summaries.
It is recommended that summary tables for the nonclinical information in the Common Technical Document be provided in the format outlined in this Guideline.

Applicants can modify the format if needed to provide the best possible presentation of the information and to facilitate the understanding and evaluation of the results.
This Guideline is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed.

Applicants might need to add some items to or delete some items from the cited format where appropriate. One tabular format can contain results from several studies.
Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.

This Guideline is not intended to indicate what studies are requested, but solely to advise how to tabulate study results if a study is performed.
Applicants might need to add some items to or delete some items from the cited format where appropriate. One tabular format can contain results from several studies. Alternatively, it may be appropriate to cite the data resulting from one study in several tabular formats.

The recommended formats for the tables in the Nonclinical Tabulated Summaries are follows

ICH guidelines. However, it is the responsibility of the applicant to decide on the best possible presentation of the data for each product.

Authors should keep in mind that, in some regions, a review of the Tabulated Summaries (in conjunction with the Written Summaries) represents the primary review of the nonclinical information.

Presentation of the data in the formats provided as templates and examples should ensure that a sufficient level of detail is available to the reviewer and should provide concise overviews of related information.

When a juvenile-animal study has been conducted, it should be tabulated using the template appropriate for the type of study.

The order of presentation given for the Nonclinical Written Summaries should be followed for the preparation of the tables for the Nonclinical Tabulated Summaries.

For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.
For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

2.4.1.2. CLINICAL OVERVIEW

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them.

Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information.

The clinical Overview should be presented in the following sequence.

2.4.1.2. 1.Product Development Rationale

The discussion of the rationale for the development of the FPP/VPP should:

(a) Identify the pharmacological class of the FPP/VPP;
(b) Describe the particular clinical/pathophysiological condition that the FPP/VPP is intended to treat, prevent, or diagnose (the targeted indication);
(c) Briefly summarise the scientific background that supported the investigation of the FPP/VPP for the indication(s) that was (were) studied;
(d) Briefly describe the clinical development programme of the FPP/VPP including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme;
(e) Note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies. Pertinent

published literature should be referenced;

(f) Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented. Formal advice documents (e.g., official meeting minutes, official guidance, and letters from regulatory authorities) should be referenced, with copies included in the references section of Module 5.

2.4.1.2. 2. Overview of Bio-pharmaceutics

The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).

2.4.1.2. 3.Overview of Clinical Pharmacology

The purpose of this section is to present a critical analysis of the pharmacokinetic (PK), pharmacodynamic (PD), and related in vitro data in the CTD. The analysis should consider all relevant data and explain why and how the data support the conclusions drawn. It should emphasise unusual results and known or potential problems, or note the lack thereof. This section should address:

(a) Pharmacokinetics of FPP/VPP;

(b) Pharmacodynamics of FPP/VPP.

Interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies should be summarised in clinical summary.

2.4.1.2. 4.Overview of Efficacy

The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the FPP/VPP in the intended population.

The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information.

Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided.

Prematurely terminated studies should be noted and their impact should be considered. The following issues should generally be considered: Relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly. Differences between the studied population(s) and the population that would be expected to receive the FPP/VPP after marketing should be discussed.

Implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified. Validation of any scales used should be discussed.

Statistical methods and any issues that could affect the interpretation of the study results (e.g., important modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol; Support for any unplanned analyses; procedures for handling missing data; and corrections for multiple endpoints). Similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.

Observed relationships between efficacy, dose, and dosage regimen for each indication should be provided Support for the applicability to the new region of data generated in another region, where appropriate for products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.

Data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.

The clinical relevance of the magnitude of the observed effects. If surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.
Efficacy in special populations: If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

2.4.1.2. 5. Overview of Safety
The purpose of this section is to provide a concise critical analysis of the safety data, noting how results support and justify proposed prescribing information.
A critical analysis of safety should consider the following: Adverse effects characteristic of the pharmacological class; and approaches taken to monitor for similar effects should be described.

Special approaches to monitoring for particular adverse events: Relevant animal toxicology and product quality information, findings that affect or could affect the evaluation of safety in clinical use should be considered.
Limitations of the safety database, e.g., related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.

Common and non-serious adverse events, with reference to the tabular presentations of events, the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members of the therapeutic class. Events that are substantially more or less common or problematic (considering the duration and degree of the observed events) with the test drug than with active controls are of particular interest.
Serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the

product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.

Similarities and differences in results among studies, and their effect upon the interpretation of the safety data. Any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism. Relation of adverse events to dose, dose regimen, and treatment duration.

Long-term safety (E1a).
Methods to prevent, mitigate, or manage adverse events. Reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues.
World-wide marketing experience. The extent of the world-wide experience should be briefly discussed:

(a) Any new or different safety issues identified;
(b) Any regulatory actions related to safety;
(c) Support for the applicability to the new region of data generated in another region, where appropriate.

2.4.1.2. 6. Benefits and Risks Conclusions
The purpose of this section is to integrate all of the conclusions reached in the previous sections about the bio pharmaceutics, clinical pharmacology, efficacy and safety of the FPP/VPP and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information.

This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.
This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

(a) The efficacy of the FPP/VPP for each proposed indication;
(b) Significant safety findings and any measures that may enhance safety;
(c) Dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens;
(d) Efficacy and safety in sub-populations, e.g., those defined by age, organ function, disease severity, and genetic polymorphisms;
(e) Any potential effect of the FPP/VPP that might affect ability to drive or operate heavy machinery.

Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include: The drug is for treatment of a non-fatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, pro-arrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity.

Safe and/or effective use of the drug requires potentially difficult selection or management

approaches that require special Veterinarian expertise.

2.4.1.2. 7. Literature References
A list of references used, stated in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE)*or the system used in ― Chemical Abstracts, should be provided. Copies of all references cited in the Clinical Overview should be provided in Section 5.1.4 of Module 5.

2.4.1.3. Clinical Summary

The Clinical Summary is intended to provide a detailed, factual summarization of all of the clinical information in the Common Technical Document.
The comparisons and analyses of results across studies provided in this document should focus on factual observations.

In contrast, the Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The following order is recommended:
2.4.1.3. 1. Summary of Biopharmaceutics Studies and Associated Analytical Methods
For generic products, Overview, summaries and conclusion should be filled in Bioequivalence Trial Information Summary.

2.4.1.3. 1.1. Background and Overview

This section should provide to the reviewer with an overall view of the formulation development process, the in vitro and in vivo dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and in vitro dissolution profile database. Reference should be made to any guidelines or literature used in planning and conducting the studies.

This section should also provide to the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision). This section should not include detailed information about individual studies.

2.4.1.3. 1.2. Summary of Results of Individual Studies

A tabular listing of all biopharmaceutical studies should generally be provided, together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important in vitro or in vivo data and information relevant to BA and BE. The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results. Similar studies may be described together, noting the individual study results and any important differences among the studies.

2.4.1.3. 1.3. Comparison and Analyses of Results Across Studies

This section should provide a factual summary of all in vitro dissolution, BA, and comparative BA studies carried out with the drug substance or drug product(VPP), with particular attention to differences in results across studies. This overview should typically summarize the findings in text and tables and should consider the following:
Evidence of the effects of formulation and manufacturing changes on in vitro dissolution and BA and conclusions regarding BE.

When manufacturing or formulation changes are made for products containing complex drug substances (e.g., a protein), pharmacokinetic (PK) studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes.
Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product (VPP). Nonetheless, such studies should be reported in this section.
Note also that PK studies alone may not be sufficient to assure similarity between such drug products. In many situations, pharmacodynamic (PD) studies or clinical trials may be necessary.

Additionally, depending on the circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier.

Evidence of correlations between in vitro dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications. Comparative bioavailability, including BE conclusions, for different dosage form strengths. Comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed. The source and magnitude of observed inter- and intra-subject variability for each formulation in a comparative BA study.

2.4.2 GENERIC DRUG APPLICATIONS ONLY

2.4.2.1 CLINICAL OVERVIEW AND CLINICAL SUMMARY

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document.

The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarisation of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).

The Clinical Overview is primarily intended for use by regulatory agencies in the review of the

clinical section of a marketing application. It should also be a useful reference to the overall clinical findings for regulatory agency staff involved in the review of other sections of the marketing application.

The Clinical Overview should present the strengths and limitations of the development program and study results, analyse the benefits and risks of the medicinal product in its intended use, and describe how the study results support critical parts of the prescribing information.

In order to achieve these objectives, the Clinical Overview should:

(a) Describe and explain the overall approach to the clinical development of a medicinal product, including critical study design decisions;
(b) Assess the quality of the design and performance of the studies, and include a statement regarding GCP compliance;
(c) Provide a brief overview of the clinical findings, including important limitations (e.g., lack of comparisons with an especially relevant active comparator, or absence of information on some patient populations, on pertinent endpoints, or on use in combination therapy);
(d) Provide an evaluation of benefits and risks based upon the conclusions of the relevant clinical studies, including interpretation of how the efficacy and safety findings support the proposed dose and target indication and an evaluation of how prescribing information and other approaches will optimise benefits and manage risks;
(e) Address particular efficacy or safety issues encountered in development, and how they have been evaluated and resolved;
(f) Explore unresolved issues, explain why they should not be considered as barriers to approval, and describe plans to resolve them;
(g) Explain the basis for important or unusual aspects of the prescribing information;
(h) The Clinical Overview should generally be a relatively short document (about 30 pages). The length, however, will depend on the complexity of the application. The use of graphs and concise tables in the body of the text is encouraged for brevity and to facilitate understanding;
(i) It is not intended that material presented fully elsewhere be repeated in the Clinical Overview;
(j) Cross-referencing to more detailed presentations provided in the Clinical Summary or in Module 5 is encouraged.

2.4.2.1.1 Product Development Rationale

The discussion of the rationale for the development of the medicinal product should:

(a) identify the pharmacological class of the medicinal product;
(b) Describe the particular clinical/pathophysiological condition that the medicinal product is intended to treat, prevent, or diagnose (the targeted indication);
(c) Briefly summarise the scientific background that supported the investigation of the medicinal product for the indication(s) that was (were) studied;
(d) Briefly describe the clinical development programme of the medicinal product, including ongoing and planned clinical studies and the basis for the decision to submit the application at this point in the programme. Briefly describe plans for the use of foreign clinical data (ICH E5);
(e) Note and explain concordance or lack of concordance with current standard research

approaches regarding the design, conduct and analysis of the studies.

Pertinent published literature should be referenced. Regulatory guidance and advice (at least from the region(s) where the Clinical Overview is being submitted) should be identified, with discussion of how that advice was implemented. Formal advice documents (e.g., official meeting minutes, official guidance, letters from regulatory authorities) should be referenced, with copies included in the references section of Module 5.

2.4.2.1.2 Overview of Biopharmaceutics studies

The purpose of this section is to present a critical analysis of any important issues related to bioavailability that might affect efficacy and/or safety of the to-be-marketed formulation(s) (e.g., dosage form/strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).

2.4.2.1.3 Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.4.2.1.3.1 Background and Overview

This section should provide the reviewer with an overall view of the formulation development process, the in vitro and in vivo dosage form performance, and the general approach and rationale used in developing the bioavailability (BA), comparative BA, bioequivalence (BE), and in vitro dissolution profile database.

Reference should be made to any guidelines or literature used in planning and conducting the studies. This section should also provide the reviewer with an overview of the analytical methods used, with emphasis on the performance characteristics of assay validation (e.g., linearity range, sensitivity, specificity) and quality control (e.g., accuracy and precision).

This section should not include detailed information about individual studies.

2.4.2.1.3.2 Summary of Results of Individual Studies

A tabular listing of all biopharmaceutic studies should generally be provided, together with narrative descriptions of relevant features and outcomes of each of the individual studies that provided important in vitro or in vivo data and information relevant to BA and BE.

The narrative descriptions should be brief, e.g., similar to an abstract for a journal article, and should describe critical design features and critical results.

Similar studies may be described together, noting the individual study results and any important differences among the studies.

These narratives may be abstracted from the ICH E3 synopsis. References or electronic links to the full report of each study should be included in the narratives.

2.4.2.1.3.3 Comparison and Analyses of Results Across Studies

This section should provide a factual summary of all in vitro dissolution, BA, and comparative BA studies carried out with the drug substance or drug product, with particular attention to differences in results across studies.

This overview should typically summarise the findings in text and tables and should consider the following:

(a) Evidence of the effects of formulation and manufacturing changes on in vitro dissolution

and BA and conclusions regarding BE. When manufacturing or formulation changes are made for products containing complex drug substances (e.g., a protein), pharmacokinetic (PK) studies comparing the product before and after the changes may be performed to ensure that the PK characteristics have not changed as a result of product changes;

(b) Although such studies are sometimes referred to as BE studies, they generally do not focus on assessing release of drug substance from drug product. Nonetheless, such studies should be reported in this section. Note also that PK studies alone may not be sufficient to assure similarity between such drug products. In many situations, pharmacodynamic (PD) studies or clinical trials may be necessary. Additionally, depending on the circumstances, antigenicity data may also be needed. Results of these other types of studies, when they are needed, should be reported in the appropriate places in the dossier;

(c) Evidence of the extent of food effects on BA and conclusions regarding BE with respect to meal type or timing of the meal (where appropriate);

(d) Evidence of correlations between in vitro dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications;

(e) Comparative bioavailability, including BE conclusions, for different dosage form strengths;

(f) Comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed;

(g) The source and magnitude of observed inter- and intrasubject variability for each formulation in a comparative BA study.

2.4.2.1.4 Overview and summary of in-vitro dissolution tests complementary to bioequivalence studies.

Provide a brief overview and summary of the results of in vitro dissolution tests at three different buffers (normally pH 1.2, 4.5 and 6.8) and the media intended for drug product release (QC media), obtained with the batches of test and reference products that were used in the bioequivalence study should be reported.

Particular dosage forms like ODT (oral dispersible tablets) may require investigations using different experimental conditions. The results should be reported as profiles of percent of labelled amount dissolved versus time displaying mean values and summary statistics.

2.4.2.1.5 Overview and summary in-vitro dissolution tests in support of biowaiver of strengths

Provide an overview and summary to justify for waiving of bioequivalence testing.

MODULE 3: QUALITY INFORMATION

This module is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug products.

Table of Contents of the Quality part should be provided. A Table of Contents should be provided that lists all of the reports and gives the location of each study report in the Common Technical Document.

3.1. Body of Data

The "Body of Data" in this guideline merely indicates where the information should be located. Neither the type nor extent of specific supporting data has been addressed in this guideline.

3.2. S Active Substance(S)

The information on the API (active substance) can be submitted to Rwanda FDA according to the following options:

Option 1: Provide the latest, valid European Certificate of Suitability (CEP) with all annexes;

Option 2: Full Details in the Product Dossier;

Option 3: Provide a Drug Master File(s) [DMF(s)] submitted by the API manufacturer;

Option 4: Active pharmaceutical ingredient pre-qualified by relevant UN Agencies.

For a drug product containing more than one drug substance, the information requested for module 3 labelled Active Pharmaceutical Ingredient(S) [API(s)] should be provided in its entirety for each active substance.

The applicant should clearly indicate at the beginning of the active substance section (in the PD and in the QOS-PD) how the information on the active substance for each active substance manufacturer is being submitted. The active substance information submitted by the applicant/VPP manufacturer should include the following for each of the options used.

Option 1: Certificates of Suitability of the European Pharmacopoeia (CEP)

A Copy of the latest version of Certificate (s) of Suitability of the European Pharmacopoeia (CEP) (including any annexes) should be provided where applicable in module 1. The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the VPP manufacturer or applicant to Rwanda FDA who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform Rwanda FDA in the event that the CEP is withdrawn.

It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1. Along with the CEP the applicant should supply the following information in the dossier, with data summarized in the QOS-PD:

3.2. S. General properties

Discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and EP monograph, e.g. solubilities and polymorphs as per guidance in this section.

3.2. S.1. Elucidation of structure and other characteristics

Studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.

3.2. S.2. Specification

The specifications of the VPP manufacturer including all tests and limits of 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.

3.2. S.3.Analytical procedures and validation

For any tests in addition to those in the CEP and Ph.Eur monograph.

3.2. S.4. Batch analysis

Results from two batches of at least pilot scale, demonstrating compliance with the VPP manufacturer's API specifications.

3.2. S.5. Reference standards or materials

Information on the FPP manufacturer's reference standards.

3.2. S.6. Container-closure system

Specifications including descriptions and identification of primary packaging components.

3.2. S.7.Stability

Exception: where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant. In the case of sterile APIs, data on the sterilization process of the API, including validation data, should be included in the PD.

Option 2: Full Details in the Product Dossier

Full details on the API information submitted by the API manufacturer, provided that the APIMF contains all information listed under Module 3 including details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the FPP/VPP dossier as outlined in the subsequent sections of this guideline.

3.2. S.1 General information

3.2. S. 1.1. Nomenclature

Information on the nomenclature of the API should be provided.

For example:

(a) (Recommended) 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 Adopted Name
(f) (USAN), British Approved Name (BAN));
(g) Chemical Abstracts Service (CAS) registry number.

The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labelling information (e.g. summary of product characteristics, package leaflet, labelling). Where several names exist, the preferred name should be indicated.

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. For APIs existing as salts, the molecular mass of the free base or acid should also be provided.

3.2. S.1.3. General properties

A list should be provided of physicochemical and other relevant properties of the API.
This information can be used in developing the specifications, in formulating FPPs/VPPs and in the testing for release and stability purposes.
The physical and chemical properties of the API should be discussed including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), 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 APIs are discussed below in greater detail.

a) Physical description

The description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous.

Solubilities/quantitative aqueous pH solubility profile
The following should be provided for all options for the submission of API data.
The solubilities in a number of common solvents should be provided (e.g. water, alcohols, dichloromethane, and acetone).

The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media should be provided in mg/ml. If this information is not readily available (e.g. literature references), it should be generated in-house.
For solid oral dosage forms, the dose/solubility volume should be provided as determined by:

$$\text{Dose/solubility volume} = \frac{\text{Largest dosage strength (mg)}}{\text{The minimum concentration of the drug (mg/ml)}}$$

corresponding to the lowest solubility determined over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5 °C).

As per the Biopharmaceutics Classification System (BCS), highly soluble (or highly water-soluble) APIs are those with a dose/solubility volume of less than or equal to 250 ml.

For example, compound A has as its lowest solubility at 37 ± 0.5 °C, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a BCS highly soluble API as its dose/solubility volume is greater than 250 ml (400 mg/1.0 mg/ml = 400 ml).

b) Polymorphism

The polymorphic form(s) present in the proposed API should be listed in section 3.2.S.3;

The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant; the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1; and if a polymorphic form is to be defined or limited (e.g. for APIs that are not BCS highly soluble and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1 through 3.2.S.4.5.

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

c) Particle size distribution

Studies performed to identify the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of this guideline for additional information).

Information from literature should be provided.
Supportive data and results from specific studies or published literature can be included within or attached to this section.

3.2. S.2. Manufacture

3.2. S.2.1 Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.

The facilities involved in the manufacturing, packaging, labelling, testing and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API) it should be clearly indicated.
The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address (es) should be provided.
A valid manufacturing authorization should be provided for the production of APIs. If available, a certificate of GMP compliance should be provided in the PD Module 1.

3.2. S.2.2 Description of manufacturing process and process controls

The description of the API 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. For example, a flow diagram of the synthetic process (es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g. temperature, pressure, pH, and time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.2. S.2.5.

The API starting material should be fully characterized with respect to identity and purity. The starting material for synthesis defines the starting point in the manufacturing process for an API to be described in an application. The applicant should propose and justify which substances should be considered as starting materials for synthesis. See section 3.2.S.3 for further guidance.

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 API manufacturer, 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 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. Alternate processes should be 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 S.3.2.

2. S.2.3 Control of materials

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided.
Information demonstrating that materials meet standards appropriate for their intended use should be provided.
In general, the starting material for synthesis described in the marketing authorization dossier should:

(a) be a synthetic precursor of one or more synthesis steps prior to the final API intermediate acids, bases, salts, esters and similar derivatives of the API, as well as the racemate of a single enantiomer API, are not considered final intermediates;
(b) be a well characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);
(c) have well-defined specifications that include among others one or more specific identity tests and limits for assay and specified, unspecified and total impurities; and
(d) be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials.
Confirmation should be provided that the specifications apply to materials used at each manufacturing site.

A certificate of analysis of the starting material for synthesis should be provided. A summary of the information on starting materials should be provided in the QOS- PD.

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

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are without risk of transmitting agent of animal spongiform encephalopathies.

3.2. S.2. 4. Controls of critical steps and intermediates

Critical steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 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.
The critical steps should be identified and these steps can be among others:

(a) steps where significant impurities are removed or introduced;
(b) steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation;
(c) steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

3.2. S.2. 5. Process validation and/or evaluation

Process validation and/or evaluation studies for aseptic processing and sterilization should be included. It is expected that the manufacturing processes for all APIs are properly controlled. If the API is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilization methods.

The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternate processes should be justified and described.

3.2. S.2.6. Manufacturing Process Development

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

3.2. S.3. Characterization

3.2. S.3.1. Elucidation of structure and other characteristics

Confirmation of structure based on e.g. synthetic route and spectral analyses should be provided. Information such as the potential for isomerism, the identification of stereochemistry or the potential for forming polymorphs should also be included.
Elucidation of structure shall be included.

The PD should include quality assurance (QA) certified copies of the spectra, peak assignments and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the API. The QOS should include a list of the studies performed and a conclusion from the studies (e.g. if the results support the proposed structure).

For APIs that are not described in an officially recognized pharmacopoeia, the studies carried out to elucidate and/or confirm the chemical structure normally include elemental analysis, infrared (IR), ultraviolet (UV), nuclear magnetic resonance (NMR) and mass spectra (MS) studies. Other tests could include X-ray powder diffraction and differential scanning calorimetry (DSC).
For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient

to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with a pharmacopoeial reference standard.

a) Isomerism/Stereochemistry

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identity of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.
The potential for inter-conversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.
When a single enantiomer of the API is claimed for non-pharmacopoeial APIs, unequivocal proof of absolute configuration of asymmetric centres should be provided such as determined by X-ray of a single crystal.

If, based on the structure of the API, there is not a potential for stereoisomerism, it is sufficient to include a statement to this effect.

b) Polymorphism

Many APIs can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an API to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice.

Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or non-stoichiometric amounts of a solvent. If the incorporated solvent is water the solvents are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API process ability, pharmaceutical product manufacturability and product quality/performance, including stability, dissolution and bioavailability.
Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not BCS highly soluble.

In the absence of published data for APIs that are not BSC highly soluble, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form.
Polymorphic screening is generally accomplished via crystallization studies using different

solvents and conditions.

There are a number of methods that can be used to characterize the polymorphic forms of an API; Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism.
X-Ray diffraction can also be used to provide unequivocal proof of polymorphism.
Other methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, solid-state nuclear magnetic resonance (ssNMR]) is helpful to further characterize polymorphic forms.
Where polymorphism is a concern, the applicants/ manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.
Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the API is used in a solvated form, the following information should be provided:
Specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
Specifications for the solvated API including appropriate limits on the weight ratio API to solvent (with data to support the proposed limits);
A description of the method used to prepare the solvate in 3.2. S.2.2. Particle size distribution.

For APIs whose particle size distribution will have influence on FPP process ability, stability, content uniformity, dissolution and bioavailability, specifications should include controls on the particle size distribution.

3.2. S.3.2 Impurities

Information on impurities should be provided.
Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C impurity guidelines. Additional information to provide further guidance on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeia standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture, or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins. The discussion of pharmacopoeia APIs should not be limited to the impurities specified in the API monograph.

Identification of impurities shall be included.

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendial monograph.
As a result, each product dossier is assessed independently to consider the potential impurities that may arise from the proposed route(s) of synthesis.
For these reasons, the ICH limits for unspecified impurities (e.g. NMT 0.10% or 1.0 mg per day intake (whichever is lower) for APIs having a maximum daily dose =2 g/day) are generally

recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph that could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an officially recognized pharmacopoeia is generally considered to be qualified.
The following is an additional option for qualification of impurities in existing APIs:The limit for an impurity present in an existing API can be accepted by comparing the impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g. comparative HPLC studies). If samples of the innovator product are not available, the impurity profile may also be compared to a different prequalified FPP with the same route of administration and similar characteristics (e.g. tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g. age of samples) to obtain a meaningful comparison of the impurity profiles.

Levels of impurities generated from studies under accelerated or stressed storage conditions of the innovator or prequalified FPP are not considered acceptable/qualified.

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or prequalified FPP.

3.2. S.4 Control of the API

3.2. S.4.1 Specification

The specification for the API should be provided.
Copies of the API specifications, dated and signed by authorized personnel (e.g. the person in charge of the quality control or quality assurance department) should be provided in the marketing authorization dossier, including specifications from each API manufacturer as well as those of the FPP/ manufacturer.

The FPP manufacturer's API specification should be summarized according to the table in the QOS template under the headings tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods):

The standard declared by the applicant could be an officially recognized compendial standard (BP, JP, Ph.Eur, Ph.Int. and USP) or a house (manufacturer's) standard.
The specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.

For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC, laser diffraction), the source refers to the origin of the analytical procedure (BP, JP, Ph. Eur, Ph. Int, USP, in-house) and the version (e.g. code number/version/date) should be provided for version control purposes.
In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each

manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g. in the case of residual solvents).
Any non-routine testing should be clearly identified as such and justified along with the proposal on the frequency of non-routine testing.

3.2. S.4.2 Analytical procedures

The analytical procedures used for testing the API should be provided. Copies of the in-house analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendial analytical procedures.

3.2. S.4.3 Validation of analytical procedures

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

Copies of the validation reports for the analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided.

Tables should be used to summarize the validation information of the analytical procedures of the FPP manufacturer for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS.

The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS.
The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore, the monograph and compendial method should be demonstrated suitable to control the impurity profile of the API from the intended source(s).

In general verification is not necessary for compendial API assay methods. However, specificity of a specific compendial assay method should be demonstrated if there are any potential impurities that are not specified in the compendial monograph. If an officially recognized compendial method is used to control API-related impurities that are not specified in the monograph, full validation of the method is expected with respect to those impurities.

If an officially recognized compendial standard is claimed and an in-house method is used in lieu of the compendial method (e.g. for assay or for specified impurities), equivalency of the in-house 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 impurity methods, the sample analysed should be the API spiked with impurities at concentrations equivalent to their specification limits.

3.2. S.4.4 Batch analyses

Description of batches and results of batch analyses should be provided.
The information provided should include batch number, batch size, date and production site of relevant API batches.

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP/VPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. This data is used to evaluate consistency in API quality. The FPP/VPP manufacturer's test results should be summarized in the QOS.

For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as "within limits" or "conforms". A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

3.2. S.4.5 Justification of specification

Justification for the API specification should be provided.
A discussion should be provided on the inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized compendial standard(s), etc. If the officially recognized compendial methods have been modified or replaced, a discussion should be included.

The justification for certain tests, analytical procedures and acceptance criteria may have been discussed in other sections of the PD (e.g. impurities, particle-size distribution) and does not need to be repeated here, although a cross-reference to their location should be provided.

Refer to ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, for more guidance

3.2. S.5 Reference standards or materials

Information on the reference standards or reference materials used for testing of the API should be provided. Information should be provided on the reference standard(s) used to generate data in the PD, as well as those to be used by the FPP/VPP manufacturer in routine API and FPP/VPP testing.

The source(s) of the reference standards or materials used in the testing of the API should be provided (e.g. those used for the identification, purity, and 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 (BP, JP, Ph. Eur, Ph. Int, USP) where one exists and the lot number should be provided. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise, a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, NMR, MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water-/solvent-free basis). Absolute content of the primary reference standard must be declared and should follow the scheme:

100% minus organic impurities (quantitated by an assay procedure, e.g. HPLC, DSC, etc.) minus inorganic impurities, minus volatile impurities by loss on drying (or water content minus residual solvents).

A secondary (or in-house) reference standard can be used by establishing it against a suitable primary reference standard, e.g. by providing legible copies of the IR of the primary and secondary reference standards run concomitantly and by providing its certificate of analysis, including assay determined against the primary reference standard. A secondary reference standard is often characterized and evaluated for its intended purpose with additional procedures other than those used in routine testing (e.g. if additional solvents are used during the additional purification process that are not used for routine purposes).

3.2. S.6 Container-closure system

A description of the container-closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications.
The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non compendial methods (with validation) should be included, where appropriate.
For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.
The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including absorption to container and leaching, and/or safety of materials of construction.
Primary packaging components are those that are in direct contact with the API or FPP/VPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR).

Copies of the labels applied on the secondary packaging of the API should be provided and should include the conditions of storage. In addition, the name and address of the manufacturer of the API should be stated on the container, regardless of whether re-labelling is conducted at any stage during the API distribution process.

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 summarised. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions.
With respect to storage conditions and re-test date or shelf life, as appropriate.

The purpose of stability testing is to: "Provide evidence of how the quality of an active substance or VPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light."
The tables in the QOS-PD template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions, commitments).

Stress testing

Stress testing of the active substance can help to identify the likely 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 and the type of VPP 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 or VPP is placed in solution expediently, for example, under the conditions shown in the following table.

Stress factor	Conditions
Heat	60°C
Humidity	75% RH or greater
Acid	0.1N HCl
Base	0.1N NaOH
Oxidative	3% H2O2
Photolytic	Metal halide, Hg Xe lamp, or UV-B/fluorescent
Metal ions (optional)	0.05 M Fe2+ or Cu2+

The objective is not to completely degrade the active compound but to generate degradation to a small extent, typically 10-30% loss of active by assay when compared with non-degraded compound. This target is chosen so that some degradation occurs, but it is not so severe that secondary products are generated. (Secondary degradation products are degradation products of degradation products and in most cases, are not observed during stability studies.) 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.

Stress testing is to be carried out on a single batch of the active substance. 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. Because of the harsher conditions, these compounds may not be observed under the accelerated stress studies. However, this approach serves to generate degradation products that can be used as a worst case to assess the analytical method performance.

Examining degradation products under stress conditions is also useful in developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions. Results from these studies form an integral part of the information provided to Rwanda FDA.

For active substances not described in an official pharmacopoeial 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 no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to the Rwanda FDA.

Reference: VICH GL5 Photostability Testing of New Veterinary Drug Substances and Medicinal Products.

3.2. S.7. 2. Accelerated and long-term stability testing

Available information on the stability of the API under accelerated and long-term conditions should be provided, including information in the public domain or obtained from scientific literature. The source of the information should be identified. The required long-term storage conditions for APIs for the registration of the product is either 30ºC±2ºC/65%±5%RH or 30ºC±2ºC/75%±5%RH. Studies covering the proposed retest period at the above-mentioned long-term storage conditions will provide better assurance of the stability of APIs at the conditions of the supply chain corresponding to the Rwandan environmental conditions (i.e. Zone IV).

Alternative conditions should be supported with appropriate evidence, which may include literature references or in-house studies, demonstrating that storage at 30 ºC is inappropriate for the API. To establish the retest period, data should be provided on not less than three batches of at least pilot scale. The batches should be manufactured by the same synthesis route as production batches and using a method of manufacture and a procedure that simulates the final process to be used for production batches. The stability testing programme should be summarized and the results of stability testing should be summarized in the dossier and in the

tables in the QOS-PD.

The information on the stability studies should include details such as storage conditions, batch number, batch size, container-closure system and completed (and proposed) test intervals.

The minimum data required at the time of submitting the dossier are shown below:

Storage condition	Temperature	Relative Humidity (%)	Minimum Time Period (Months)
Accelerated	40 ^{0}C ±20C	75%±5%.	6
Intermediate	30 ^{0}C ±20C	65%±5%	6
Long-term	30 ^{0}C ±20C	65%±5%.	12

3.2. S.7. 3. Stability Data

Results of the stability studies (e.g., forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical, or narrative.

Information on the analytical procedures used to generate the data and validation of these procedures should be included.
The actual stability results used to support the proposed retest period should be included in the dossier. For quantitative tests (e.g. individual and total degradation product tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms”.

References

VICH GL3 (R) –Stability testing of the new veterinary substances and medicinal products,

Option 3: Drug Master File (DMF)

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the active substance may be submitted as a DMF by the active substance manufacturer. In such cases, the Open part (non-proprietary information) needs to be included in its entirety in the PD as an annex to 3. S.1. In addition, the applicant/VPP manufacturer should complete the following sections in the PD and QOS-PD in full according to the guidance provided unless otherwise indicated in the respective sections:

(a) General information S.1.1 through S.1.3;
(b) Manufacture S.2;
(c) Manufacturer(s) S.2.1;
(d) Description of manufacturing process and process controls S.2.2;
(e) Controls of critical steps and intermediates S.2.4;
(f) Elucidation of structure and other characteristics S.3.1;
(g) Impurities S.3.1;

(h) Control of the active substance S.4.1 through S.4.5;
(i) Reference standards or materials S.5;
(j) Container closure system S.6;
(k) Stability S.7.1 through S.7.3.

It is the responsibility of the applicant to ensure that the complete DMF (i.e. both the applicant's Open part and the active substance manufacturer's restricted part) is supplied to Rwanda FDA directly by the active substance manufacturer and that the applicant has access to the relevant information in the DMF concerning the current manufacture of the active substance.

A copy of the letter of access should be provided in the Module 1.

DMF holders can use the guidance provided for the option "Full details in the PD" for preparation of the relevant sections of the Open and Restricted parts of their DMFs.

3.2. P VETERINARY PHARMACEUTICAL PRODUCT(s) (VPP) (s)

3.2. P.1 Description and Composition of the VPP

3.2. P.1.1. Description of the dosage form

The description of the VPP should include the physical description, available strengths, release mechanism (e.g. immediate, long acting injection), as well as any other distinguishable characteristics, e.g.
"The proposed X 100mg bolus is available as white, oval, film-coated tablets, debossed with '100' on one side and a break-line on the other side.

3.2. P.1.2 Composition

List of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications).

The tables in the QOS template should be used to summarize the composition of the VPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and percentage basis, including a statement of the total weight or measure of the dosage unit. The individual components for mixtures prepared in-house (e.g. coatings) should be included in the tables, where applicable.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the VPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated. All overages should be clearly indicated (e.g. "contains 2% overage of the active substance to compensate for manufacturing losses").

The components should be declared by their proper or common names, quality standards (e.g.

BP, House) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilised, emulsified).

The function of each component (e.g. diluent/filler, binder, disintegrant, lubricant, glidant, granulating solvent, coating agent, antimicrobial preservative) should be stated. If an excipient performs multiple functions, the predominant function should be indicated.

The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends, imprinting inks).

This information (excluding the solvents) is to be listed in the product information (e.g. prescribing information leaflet, User information leaflet and labelling). Description of accompanying reconstitution diluent(s).

For VPPs supplied with reconstitution diluent(s) that are commercially available or have been assessed and considered acceptable in connection with another PD with the Rwanda FDA, a brief description of the reconstitution diluents(s) should be provided.

For VPPs supplied with reconstitution diluent(s) that are not commercially available or have not been assessed and considered acceptable in connection with another PD with the Rwanda FDA, information on the diluent(s) should be provided in a separate VPP portion ("3.2.P"), as appropriate.

3.2. P.1 3. Type of container and closure used for the dosage form and accompanying reconstitution diluents, if applicable

The container closure used for the VPP (and accompanying reconstitution diluents, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container closure system, e.g. "The product is available in HDPE bottles with polypropylene caps (in sizes of, 50's and 100's) and in PVC/Aluminium foil unit dose blisters (in packages of 2's (blister of 2 x1, 10 blisters per package)".
Reference documents: ICH Q6A.

3.2. P.2. Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application.
The studies described here are distinguished from routine control tests conducted according to specifications. Additionally, this section should identify and describe the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and VPP quality.
Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

(a) The definition of 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;
(b) Identification of the potential critical quality attributes (CQAs) of the VPP so as to adequately control the product characteristics that could have an impact on quality;
(c) 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;
(d) Discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner. 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: ICH Q8).

For a discussion of additional pharmaceutical development issues specific to the development of FDCs, reference should be made to Doc. Ref. EMEA/CVMP/83804/2005, Guideline on pharmaceutical fixed combination product.

References

1. ICH Q6A guidelines
2. ICH Q8 guidelines: Pharmaceutical Development
3. ICH Q9 guidelines: Quality Risk Management
4. ICH Q10 guidelines

3.2. P.2.1. Components of the VPP

3.2. P.2.1.1 Active substance

The compatibility of the active substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, and particle size distribution, polymorphic or solid-state form) of the active substance that can influence the performance of the VPP should be discussed.
For fixed dose combinations, the compatibility of active substances with each other should be discussed. Physicochemical characteristics of the active substance may influence both the manufacturing capability and the performance of the VPP.
In general, API-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. SmPC or product leaflet) that the excipients are present in the comparator product.

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 VPP performance should be discussed relative to their respective functions. When choosing excipients, those with a compendial monograph are generally preferred. Use of excipients in concentrations outside of established ranges is discouraged and generally requires

justification.

Ranges or alternates for excipients are normally not accepted, unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine active substance with lactose) should be included to justify the choice of excipients. Specific details should be provided where necessary (e.g. use of potato or corn starch). 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 3.2. P.2.5.

3.2. P.2.2 Finished Pharmaceutical Product

3.2. P.2.2.1 Formulation Development

A brief summary describing the development of the VPP should be provided, taking into consideration the proposed route of administration and usage.

The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e., composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed, when appropriate.

If the proposed VPP is a scored tablet, the results of a study should be provided of the uniformity of dosage units of the tablet halves.

The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results.
Uniformity testing (i.e. content uniformity or weight variation, depending on the requirement for the whole tablet) should be performed on each split portion from a minimum of 10 randomly selected whole tablets.

As an illustrative example, the number of units (i.e. The splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisect tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values.

The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the VPP specification(s). The tablet description in the VPP specification and in the product information (e.g. prescribing information leaflet and user information leaflet, and labeling,) should reflect the presence of a score.

In vitro dissolution or drug release

A discussion should be included to show how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.
The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g.

apparatus, rotation speed, medium) should be provided.

Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant.
The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of a single point test or a dissolution range should be justified based on the solubility of the active substance. For slower dissolving immediate release products (e.g. Q=80% in 90 minutes), a second-time point may be warranted (e.g. Q=60% in 45 minutes).

Modified release VPPs should have a meaningful in vitro release rate (dissolution) test that is used for routine quality control. Preferably this test should possess in vitro-in vivo correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form. For extended-release VPPs, the testing conditions should be set to cover the entire time period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release).

One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 25% or ±12.5% of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

Recommendations for conducting and assessing comparative dissolution profiles can be found in annex II of this module.

3.2. P.2.2.2. Overages

Any overages in the formulation(s) described in 3.2.P.1 should be justified.
Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).
Overages for the sole purpose of extending the shelf-life of the VPP are generally not acceptable.

3.2. P.2.2.3. Physicochemical and Biological Properties

Parameters relevant to the performance of the VPP, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed. In addition to the above considerations, refractive index may be a relevant parameter for some VPPs.

3.2. P.2.3. Manufacturing Process Development

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.
Where relevant, justification for the selection of aseptic processing or other sterilization methods

over terminal sterilization should be provided. Differences between the manufacturing processes (es) used to produce comparative bioavailability or biowaiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence VPP quality and performance should be explained (e.g. wet granulation using high shear granulator).

Active substance stress study results may be included in the rationale. Any developmental work undertaken to protect the VPP from deterioration should also be included (e.g. protection from light or moisture).
The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained, in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time, granulation end-point).

A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included (ref: ICH Q8).

3.2. P.2.4. Container Closure System

The suitability of the container closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the VPP should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the VPP).

The suitability of the container closure system used for the storage, transportation (shipping) and use of any intermediate/in-process products (e.g. premixes, bulk VPP) should also be discussed.

3.2. P.2.5. Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the VPP.

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 VPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed

acceptance criteria.

A single primary stability batch of the VPP 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.

3.2. P.2.6. Compatibility

The compatibility of the VPP 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 labeling.
Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such reconstitution) that are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.
Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labeling. These studies should preferably be conducted on aged samples. Where the labeling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, sub visible particulate matter and extractable from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labeling, compatibility of admixtures needs to be demonstrated only in the specified containers.

Studies should cover the duration of storage reported in the labeling (e.g. 24 hours under controlled room temperature and 72 hours under refrigeration). Where the labeling specifies co-administration with other VPPs, compatibility should be demonstrated with respect to the principal VPP as well as the co-administered VPP (i.e. in addition to other aforementioned parameters for the mixture, the assay and degradation levels of each co- administered VPP should be reported).

3.2. P.3. Manufacture

3.2. P.3.1. Manufacturer(s)

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided.
The facilities involved in the manufacturing, packaging, labeling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be clearly indicated.
The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

For a mixture of an active substance with an excipient, the blending of the active substance with the excipient is considered to be the first step in the manufacture of the final product and therefore the mixture does not fall under the definition of an active substance. The only

exceptions are in the cases where the active substance cannot exist on its own. Similarly, for a mixture of active substances, the blending of the active substances is considered to be the first step in the manufacture of the final product. Sites for such manufacturing steps should be included in this section.

A valid manufacturing authorization for pharmaceutical production, as well as a marketing authorization, should be submitted to demonstrate that the product is registered or licensed in accordance with national requirements.

3.2. P.3.2. Batch Formula

A batch formula provided should include a list of all components of the dosage form to be used in the manufacturing process, their amounts on a per batch basis, including overages, and a reference to their quality standards.
The tables in the QOS-PD template should be used to summarize the batch formula of the VPP for each proposed commercial batch size and express the quantity of each component on a per batch basis, including a statement of the total weight or measure of the batch.
All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. Acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the VPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 kg of active ingredient base = 1.065 kg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "Contains 7 kg (corresponding to 2%) overage of the active substance to compensate for manufacturing losses").
The components should be declared by their proper or common names, quality standards (e.g. BP, In-House) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilised, emulsified).

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

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in Section 3. P.2.3.4. In certain cases, environmental conditions (e.g., low humidity for an effervescent product) should be stated.

The maximum holding time for bulk VPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days.

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.P.2.3.3).

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

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.

Reference

ICH Q8, Q9 and Q10.

3.2. P.3.4. Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria should be provided (with 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.
Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.
Examples of applicable in-process controls include:
Granulations: moisture (limits expressed as a range), blend uniformity (e.g. low dose tablets), bulk and tapped densities, particle size distribution; Solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating; Liquids: pH, specific gravity, clarity of solutions; and Parenterals: appearance, clarity, fill volume/weight, pH, filter integrity tests, particulate matter, leak testing of ampoules.

Reference

VICH GL1, VICH GL2 ICH Q6A, Q8, Q9 and Q10

3.2. P.3.5. Process Validation and/or Assessment

Description, documentation, and results of the validation and/or assessment studies should be provided for critical steps or critical assays used in the manufacturing process (e.g., validation of the sterilization process or aseptic processing or filling).

For products that meet the criteria of an established generic product, a product quality review as outlined in Annex III of this module may be submitted in lieu of the information below.
The following information should be provided for all other products:

A copy of the process validation protocol specific to this VPP, that identifies the critical equipment and process parameters that can affect the quality of the VPP and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;

A commitment that three consecutive, production-scale batches of this VPP 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 Rwanda FDA inspection team; and

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 PD in lieu of (a) and (b) above.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics.

Thus, sub visual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the following validation scheme will need to be re-validated once further scale-up is proposed after the product given Rwanda FDA approval.

The process validation protocol should include inter alia the following:

a) reference to the current master production document;
b) a discussion of the critical equipment.

The process parameters that can affect the quality of the VPP (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 or a reference to appropriate section(s) of the dossier; the methods for recording/evaluating results; and the proposed timeframe for completion of the protocol. The manufacture of sterile VPPs needs a well-controlled manufacturing area (e.g. a strictly

controlled environment, highly reliable procedures and appropriate in-process controls).

A detailed description of these conditions, procedures and controls should be provided, together with actual copies of the following standard operating procedures:

a) Washing, treatment, sterilizing and dehydrogenating of containers, closures and equipment;
b) Filtration of solutions;
c) Lyophilisation process;
d) Leaker test of filled and sealed ampoules;
e) Final inspection of the product; and
f) Sterilization cycle.

The sterilization process used to destroy or remove microorganisms is probably the single most important process in the manufacture of parenteral VPPs. 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 to be the method of choice to ensure sterility of the final VPP. Therefore, scientific justification for selecting any other method of sterilization should be provided.

The sterilization process should be described in detail and evidence 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 VPP will not be affected. Details such as for range, temperature range and peak dwell time for a VPP 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 control 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. 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 control of microbial growth. A level of contamination of less than 0.1% is considered to be acceptable.

Reference

ICH Q8, Q9 and Q10.

3.2. P.4. Control of Excipients

3.2. P.4. 1. Specifications

The specifications from the applicant or the VPP 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 VPP (e.g. solvents) and any others used in the manufacturing process

(e.g. nitrogen, silicon for stoppers).

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

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

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

3.2. P.4. 2. Analytical Procedures

The analytical procedures used for testing the excipients should be provided. Provide certificate of analysis of one batch of each excipient.

3.2. P.4. 3. Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.
Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

References

1. VICH GL1 Text on Validation of Analytical Procedures
2. VICH GL2 Validation of Analytical Procedures: Methodology (https://vichsec.org/wp-content/uploads/2024/10/gl02_st7.pdf)

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 Human or 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, and viral safety data).

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If 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 VPP are without risk of transmitting agents of animal spongiform encephalopathies.

Materials of animal origin should be avoided whenever possible. When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module1.

Reference

ICH Q5A, Q5D and Q6B.

3.2. P.4.6. Novel Excipients

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

3.2. P.5. Control of Veterinary Pharmaceutical Product

3.2. P.5.1. Specification(s)

The specification(s) for the VPP should be provided. As defined in ICH's Q6A guideline, a specification is:

(a) "A list of tests, references to analytical procedures and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which an active substance or VPP should conform to be considered acceptable for its intended use;

(b) "Conformance to specifications" means that the active substance and / or VPP, when tested according to the listed analytical procedures, will meet the listed acceptance criteria;

(c) Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities;

(d) A copy of the VPP specification(s) from the applicant (as well as the company responsible for the batch release of the VPP, if different from the applicant), dated and signed by authorized personnel (i.e. the person in charge of the quality control or quality assurance

department) should be provided in the PD;

(e) Two separate sets of specifications may be set out: after packaging of the VPP (release) and at the end of shelf-life.

The specifications should be summarized according to the tables in the QOS template including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods): The standard declared by the applicant could be an officially recognized compendial standard (e.g. Ph. Eur,) or in House (manufacturer's) standard; Specification reference number and version (e.g. revision number and/or date) should be provided for version control purposes.

For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g. Visual, IR, UV, HPLC), the source refers to the origin of the analytical procedure (e.g. Ph. Eu, BP, in-house) and the version (e.g. code number/version/date) should be provided for version control purposes. ICH's Q6A guideline outlines recommendations for a number of universal and specific tests and criteria for VPPs. Specifications should include, at minimum, tests for appearance, identification, assay, purity, pharmaceutical tests (e.g. dissolution), physical tests (e.g. loss on drying, hardness, friability, particle size, apparent density), uniformity of dosage units, identification of colouring materials, identification and assay of antimicrobial or chemical preservatives (e.g. antioxidants) and microbial limit tests.

The following information provides guidance for specific tests that are not addressed by ICH's Q6A guideline:

Fixed-dose combination VPPs (FDC-VPPs): Analytical methods that can distinguish each active substance in the presence of the other active substance(s) should be developed and validated, Acceptance criteria for degradation products should be established with reference to the active substance they are derived from. If an impurity results from a chemical reaction between two or more active substances, its acceptance limits should be calculated with reference to the worst case (the active substance with the smaller area under the curve). Alternatively the content of such impurities could be calculated in relation to their reference standards, when any one active substance is present at less than 25 mg or less than 25% of the weight of the dosage unit, a test and limit for content uniformity is required for each active substance in the VPP, when all active substances are present at equal or greater than 25 mg and equal or greater than 25% of the weight of the dosage unit, a test and limit for weight variation may be established for each active substance in the VPP, in lieu of content uniformity testing; Modified-release products: a meaningful active substance release method; Unless there is appropriate justification, the acceptable limit for the active substance content of the VPP in the release specifications is ± 5% of the label claim (i.e. 95.0-105.0%).

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.

References

(a) VICH GL39 — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Pharmaceutical Products: Chemical Substances + Decision trees;
(b) ICH Q3B, Q3C and Q6A.

3.2. P.5. 2. Analytical Procedures

The analytical procedures used for testing the VPP should be provided. Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Provide copies of compendial analytical procedures used.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods) can be found in the 2.3.R Regional information section of the QOS (i.e. 2.3.R.2).

These tables should be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the VPP.

Refer to section 3.2.S.4.2 of this guideline for additional guidance on analytical procedures.

3.2. P.5.3 Validation of Analytical Procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the VPP, should be provided.
Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the PD) as well as those proposed for routine testing should be provided.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances and dissolution of the VPP.
As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods, as published, are typically validated based on an active substance or a VPP originating from a specific manufacturer. Different sources of the same active substance or VPP 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 VPP.

For officially recognized compendial VPP 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 in-house method is used in lieu of the compendial method (e.g. for assay or for related compounds), equivalency of the in-house 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 analyzed should be the placebo spiked with related compounds at concentrations equivalent to their specification limits.

References

1. VICH GL1 Text on Validation of Analytical Procedures;
2. VICH GL2 Validation of Analytical Procedures: Methodology;
3. ICH Q2;
4. WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials.

3.2. P.5.4. Batch Analyses

A description of batches and results of batch analyses should be provided. Information should include strength and batch number, batch size, date and site of production and use (e.g. used in comparative bioavailability or biowaiver studies, preclinical and clinical studies (if relevant), stability, pilot, scale-up and, if available, production-scale batches) on relevant VPP batches used to establish the specification(s) and evaluate consistency in manufacturing.

Analytical results tested by the company responsible for the batch release of the VPP (generally, the applicant or the VPP manufacturer, if different from the applicant) should be provided for not less than three 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 PD and the company responsible for generating the testing results should be identified.

The discussion of results should focus on observations noted for the various tests, rather than reporting comments such as “all tests meet specifications”. This should include ranges of analytical results, where relevant. For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual numerical results are provided rather than vague statements such as “within limits” or “conforms” (e.g. “levels of degradation product A ranged from 0.2 to 0.4%”).

Dissolution results should be expressed at minimum as both the average and range of individual results. Recommendations for conducting and assessing comparative dissolution profiles can be found in Annex II of the module 3.

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

Reference

ICH Q3B, Q3C and Q6A.

3.2. P.5. 5. Characterization 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 of all impurities that are potential degradation products (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the active substance with other active substances (FDCs), excipients or the container closure system) and VPP process-related impurities (e.g. residual solvents in the manufacturing process for the VPP).

Reference

ICH Q3B, Q3C and Q6A.

3.2.P.5.6 Justification of Specification(s)

Justification for the proposed VPP specification(s) should be provided.

A discussion should be provided on the omission or inclusion of certain tests, evolution of tests, analytical procedures and acceptance criteria, differences from the officially recognized compendial standard(s), etc. If the officially recognized compendial methods have been modified or replaced, a discussion should be included. The justification for certain tests, analytical procedures and acceptance criteria (e.g. degradation products, dissolution method development) may have been discussed in other sections of the PD and does not need to be repeated here, although a cross-reference to their location should be provided.

ICH Q6A should be consulted for the development of specifications for VPPs.

3.2. P.6 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the VPP should be provided, if not previously provided in "3.2.S.5 Reference Standards or Materials".
See Section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of VPP degradation products, where not included in 3.2. S.5.

Reference

ICH Q6A

3.2. P.7. Container Closure System

A description of the container closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification.
The specifications should include description and identification (and critical dimensions, with drawings where appropriate).

Non-compendial methods (with validation) should be included, where appropriate.

Descriptions, materials of construction and specifications (of the company responsible for packaging the VPP, generally the VPP manufacturer) should be provided for the packaging components that are:

In direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);
Used for drug delivery (including the device(s) for multi-dose solutions, emulsions, suspensions and powders/granules for such);
Used as a protective barrier to help ensure stability or sterility; and Necessary to ensure VPP quality during storage and shipping.

Primary packaging components are those that are in direct contact with the active substance or VPP. The specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight.

For non-functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided. Suitability information should be located in 3.2. P.2.

Information to establish the suitability (e.g. qualification) of the container closure system should be discussed in Section 3.2. P.2. Comparative studies may be warranted for certain changes in packaging components (e.g. comparative delivery study (droplet size) for a change in manufacturer of dropper tips).

3.2. P.8. Stability Testing

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life. The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the active substance and the dosage form.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the data set, a cross-reference will suffice. If different methodology was used, the test procedures applied to the stability tests on the finished product should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. Characterize the possible degradants identified by stress stability testing (see 3.7.1 Stress testing (forced degradation) for details) during development pharmaceutics (compatibilities of the active substances with each other and with the excipients as well as the effect of temperature on the rate of degradation reactions). The tests for degradants should be validated to demonstrate that they are specific to the VPP being examined and are of adequate sensitivity.

Stability studies should be performed on each individual strength and container size of the

finished product unless bracketing or matrixing is applied.
Other supporting data can be provided.

Stability-indicating quality parameters

Studies should include testing of those attributes of the VPP that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.
Characteristics studied should be those in the finished product specification that are likely to be affected by storage and/or not monitored routinely at the time of manufacture, but which may be indicative of the stability/instability of the particular dosage form.

These include:
Physical characteristics (such as organoleptic properties, physical properties characteristic to the dosage form, important quality parameters, e.g., in vitro dissolution, moisture content and change of polymorphs, if relevant). As regards tablets and capsules packed with semi-permeable blister films, loss or uptake of water must be tested during stability studies. Efficacy of additives, such as antimicrobial agents, to determine whether such additives remain effective and within the accepted validated range throughout the projected shelf life;

Chemical characteristics (assay of the active substance, content of degradation products, content of other ingredients such as preservatives, antioxidants, as well as enantiomeric purity, if relevant);

Study of the container and closure interaction with the contents, when applicable.

Where the product is to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection or a concentrate for oral suspension) “in use” stability data must be submitted to support the recommended in-use storage time and conditions for those storage forms.

It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability assessment and the changes observed on storage. Any differences between the release and shelf-life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration intended for marketing. A single primary stability batch of the finished product should be tested for antimicrobial preservative effectiveness (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.

Report and discuss the results of stability testing. Organize data for all attributes separately and evaluate each attribute in the report. No statistical analysis is required if the stability data do not show variability or a trend over time.

Shelf-life acceptance criteria should be derived from consideration of all available stability information. The proposed storage conditions should be achievable in practice in Rwanda.
The summary should include conclusions with respect to in-use storage conditions and shelf life, when applicable.

Long-term studies should cover the whole shelf life. When available long- term stability data on primary batches do not cover the proposed shelf-life period granted at the time of approval, a commitment should be made in writing to continue the stability studies post approval in order to firmly establish the shelf-life period. The post-approval stability protocol should also be provided and should be the same as that for the primary batches, unless otherwise scientifically justified.

Repackaging of bulk finished product will require stability studies in the bulk container and the final container closure system. Expiration dating is linked to the manufacturing date of the dosage form.

Photostability testing

Photostability testing should be conducted on at least one primary batch of the VPP, if not included in the stress stability tests.

Reference

VICH GL5 Photostability Testing of New Veterinary Drug Substances and Medicinal Products (http://www.vichse.org/en/guidelines2.htm).

Selection of Batches
At the time of submission data from stability studies should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.
Stability data on three primary batches are to be provided. One of the three batches should be of production scale, the remaining two batches at least pilot scale. The composition, batch size, batch number and manufacturing date of each of the stability batches should be documented and the certificate of analysis at batch release should be attached.

The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Where possible, batches of the finished product should be manufactured by using different batches of the active substance.

Container Closure System
Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

Testing Frequency

At the accelerated storage condition, a minimum of three points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended.

Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

At long term storage conditions, sampling should be done at initial, 3, 6, 9, 12, 18, 24, 36 etc. months to establish the stability characteristics of the VPP.

Reduced designs, i.e., Matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

Reference

VICH GL45: Bracketing and Matrixing Designs for Stability Testing of New Veterinary Drug Substances and Medicinal product (http://www.vichse.org/en/guidelines2.htm).

Storage Conditions

In general, a VPP should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the finished product after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product.

This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at six months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

Note: in-use stability testing should be performed on at least two different batches one of which should be investigated close to the end of shelf life.

The long-term testing should cover a minimum of 12 months' duration at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to the Authority if requested.

Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

General case

Storage temperature (°C)	Relative humidity (%)	Minimum time period covered by data at submission

Accelerated: 40±2	75±5	6
Long term: 30±2	65±5	12

Note. Unless otherwise justified, 30°C ± 2°C/65% RH ± 5% RH is the long-term stability condition for products to be marketed in Rwanda.

When a "significant change" occurs at any time during 6 months' testing at the accelerated storage condition, these should be evaluated during long term stability testing.

In general, "significant change" for a finished product is defined as: A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures.

Any degradation product exceeding its acceptance criterion.
Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., colour, phase separation, hardness).

And, as appropriate for the dosage form:
Failure to meet the acceptance criterion for pH; or Failure to meet the acceptance criteria for dissolution for 12 dosage units.

Finished products packaged in impermeable containers.

Sensitivity to moisture or potential for solvent loss is not a concern for finished products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

Finished products packaged in semi-permeable containers
Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This assessment can be carried out under conditions of low relative humidity, as defined below.

Study	Storage condition	Minimum time period covered by data at submission (months)
Long term	30±2^{o}C/65±5% RH	12
Accelerated	40±2^{o}C/NMT 25±5% RH	6

Note: Unless otherwise justified, 30 ± 2^{o}C and 65 ± 5% RH is the long-term stability condition for products to be marketed in Rwanda.

Ultimately, it should be demonstrated that aqueous-based finished products stored in semi-permeable containers could withstand low relative humidity environments. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.
A 5% loss in water from its initial value is considered a significant change for a VPP packaged

in a semi-permeable container after three (3) months storage at 40 ± 2°C and NMT 25 ± 5% RH.

Assessment

A systematic approach should be adopted in the presentation and assessment of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms, hardness, LOD, etc.).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the finished product, a shelf life and label storage instructions applicable to all future batches of the finished product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient. An approach for analyzing data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion.

If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Reference

VICH-GL3 Assessment for Stability Data.

Extrapolation of data

An active substance is considered as stable if it is within the defined specifications when stored at 30 ± 2°C/65 ± 5 % RH (2 years) and 40 ± 2°C/75 ± 5 % RH (6 months).

If long term data are supported by results from accelerated studies the re- test period/shelf life may be extended beyond the end of long-term studies. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data.

Reference

VICH-GL3 Assessment for Stability Data and Core Storage Statements.

Testingconditions where stability has been shown	Required labelling statement	Additional labelling statement*, where relevant
30°C/65% RH (long term) 40°C/75% RH (accelerated)	Do not store above 30°C, or Store below 30°C	Do not refrigerate or freeze

* Depending on the pharmaceutical form and the properties of the product, there may be a risk of deterioration due to physical changes if subjected to low temperatures. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

3.2. R. REGIONAL INFORMATION

3.2. R.1 Production Documentation

3.2. R.1.1 Executed Production Documents

A minimum of two batches of at least pilot scale, or in the case of an uncomplicated VPP (e.g. immediate-release solid VPPs (with noted exceptions) or non-sterile solutions), at least one batch of at least pilot scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller should be manufactured for each strength. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch**.**

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies. Any notations made by operators on the executed production documents should be clearly legible.

If not included in the executed batch records through sufficient in process testing, data should be provided for the batch used in comparative bioavailability or biowaiver studies that demonstrate the uniformity of this batch. The data to establish the uniformity of the bio batch should involve testing to an extent greater than that required in routine quality control.

English translations of executed records should be provided where relevant.

3.2. R.1.2 Master Production Documents

Copies of the VPP master production documents should be provided for each proposed strength, commercial batch size and manufacturing site.

The details in the master production documents should include, but not be limited to, the following:

(a) master formula;

(a) dispensing, processing and packaging sections with relevant material and operational details;

(b) relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis;
(c) Identification of all equipment by, at a minimum, type and working capacity (including make, model and equipment number, where possible);
(d) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point and tablet machine speed (expressed as target and range));
(e) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity and filter integrity checks) and specifications;
(f) sampling plan with regard to the:

(i) steps at which sampling should be done (e.g. drying, lubrication and compression),
(ii) number of samples that should be tested (e.g. for blend uniformity testing of low-dose VPPs, blend drawn using a sampling thief from x positions in the blender),
(iii) frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);precautions necessary to ensure product quality (e.g. temperature and humidity control and maximum holding times);

(g) for sterile products, reference to standard operating procedures;
(h) (SOPs) in appropriate sections and a list of all relevant SOPs at the end of the document;
(i) theoretical and actual yield;
(j) compliance with the GMP requirements.

3.2.R.2 Analytical Procedures and Validation Information

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES			
HPLC Method Summary		Volume/Page:	
Method name:			
Method code:		Version and/or Date:	
Column(s) / temperature (if other than ambient):			
Mobile phase (specify gradient program, if applicable):			
Detector (and wavelength, if applicable):			
Flow rate:			
Injection volume:			
Sample solution concentration (expressed as mg/ml, let this be termed “A”):			
Reference solution concentration (expressed as mg/ml and as % of “A”):			

System suitability solution concentration (expressed as mg/ml and as % of "A"):	
System suitability tests (tests and acceptance criteria):	
Method of quantification (e.g. against ACTIVE SUBSTANCE or impurity reference standard(s)):	
Other information (specify):	

ATTACHMENT NUMBER:	

Validation Summary		Volume/Page:			
Analytes:					
Typical retention times (RT)					
Relative retention times (RTImp./RTACTIVE SUBSTANCE or Int. Std.):					
Relative response factor (RFImp./RFACTIVE SUBSTANCE):					
Specificity:					
Linearity / Range: Number of concentrations: Range (expressed as % "A"): Slope: Y-intercept: Correlation coefficient (r2) :					
ATTACHMENT NUMBER:					
Accuracy:	Conc.(s) (expressed as % "A"): Number of replicates: Percent recovery (avg/RSD):				
Precision / Repeatability: (intra-assay precision) Result (avg/RSD):	Conc.(s) (expressed as % "A"): Number of replicates:				
Precision / Intermediate Precision: (days/analysts/equipment)	Parameter(s) altered: Result (avg/RSD):				
Limit of Detection (LOD): (expressed as %					

"A")		
Limit of Quantitation (LOQ): (expressed as % "A")		
Robustness:	Stability of solutions: Other variables/effects:	
Typical chromatograms or spectra may be found in:		
Company(s) responsible for method validation:		
Other information (specify):		

3.3 Literature references

References to the scientific literature relating to both the API and VPP should be provided, if applicable.

MODULE 4: NON-CLINICAL STUDY REPORTS

4.1 Table of contents of module

4.2 Body data

Information on this part is required for all products containing new active substances. However, for products containing well established ingredients pre-clinical data is not required; instead provide literature review as prescribed in module 5.

The objective of non-clinical studies is to define the pharmacological actions (Pharmacodynamic and pharmacokinetics) and toxicological effects of the active substance in test animals and target species, users, consumers and the environments. 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:

(a) Selection of the relevant animal species;
(b) Age of the animals;
(c) Physiological state of the animals;
(d) The manner of delivery, including dose, route of administration and treatment regimen and the effect on the animals;
(e) Stability of the test material or drug under the condition of use;
(f) Safety of personnel;
(g)Environmental safety.

The safety documentation of the dossier shall show:

(a) The potential toxicity of the veterinary medicine and any dangerous effects which may occur under the proposed conditions of use in animals. These should be evaluated in relation to the severity of the pathological condition concerned;
(b) The potential harmful effects to man of residues of the veterinary medicine or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuff;
(c) The potential risks which may result from the exposure of veterinary beings to the medicinal product, for example during manufacture, in feed mixing of or on administration to the animal;
(d) The potential risks for the environment resulting from the use of the medicinal product.

Pre-clinical 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

Provide 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. 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)

Give assessment summary of action(s) other than those of therapeutic use. 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 effects, 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, sub-acute 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 74 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, sub-acute 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 veterinaries;
(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 Subacute 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 75 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 non-rodent. 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.

References

1. VICH GL31 (Safety Repeat dose); Studies to evaluate the safety of residues of veterinary drugs in human food: Repeat dose toxicity testing;
2. VICH GL37 (Safety: Repeat-dose chronic toxicity) Studies to evaluate the safety of residues of veterinary drugs in human food: Repeat-dose (chronic) toxicity testing.

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.

References

VICH GL23 (Safety Genotoxicity)-Studies to evaluate the safety of veterinary drug residues in human food: Genotoxicity testing.

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 pharmaceutical 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.

References

VICH GL28 (Safety Carcinogenicity); Studies to evaluate the safety of veterinary drug residues in human food: carcinogenicitytesting.

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/foetotoxic effects including teratogenicity

Embryotoxic/foetotoxic, including teratogenicity studies will be required:

In the case of substances or medicinal products intended for use in food-producing animals, studies of embryotoxic/foetotoxic 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.

Reference

VICH GL22 (Reproduction testing) Studies to evaluate the safety of veterinary drug residues in human food: VICH GL32 (Safety Developmental toxicity); Studies to evaluate the safety of residues of veterinary drugs in human food: Developmental toxicity testing.

4.2.1.4 Safety to users

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

4.2.1.5 Risk assessment of veterinary drugs residues in food of animal origin

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. 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. Maximum residue limits in food producing animals should be provided. All the analytical methods used should be provided.

Pre and post antimicrobial resistance surveillance should be performed on indicator pathogens e.g. E.coli, Salmonella spp.

References

1. VICH GL33 (Safety General Approach): Studies to evaluate the safety of veterinary drug residues in human food: General approach to testing;
2. VICH GL36 (Safety: General Approach); Studies to evaluate the safety of residues of veterinary drugs in human food: General approach to establish a microbiological ADI.

4.2.1.6 Toxicity to the environment

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 and likelihood of and method of excretion of the product and its active metabolites into the environment;
(b) Pattern of use and therefore quantity drug to be used (herd/flock medication or 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 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 of 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) Antihelmintics in large animals e.g. invermectins;
(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);
(f) External preparations.

Reference

1. VICH GL6 (Ecotoxicity - Phase 1) Environmental Impact Assessment (EIAs) for veterinary Pharmaceutical products (VPPs) - Phase 1;
2. VICH GL38 (Ecotoxicity Phase II); Environmental Impact Assessment (EIAs) for Veterinary Pharmaceutical Products (VPPs) - Phase II.
3. VICH GL43 (TAS Pharmaceuticals) Target Animal Safety for Pharmaceuticals.

Name and signature of the authorized person:
Date:
Official stamp

MODULE 5: CLINICAL STUDY REPORTS

5.1 Interchangeability

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

I.1 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.

(a) A cross-over 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;
(b) Studies should be done in healthy subjects or in patient if the disease affects the actions/responses studied;
(c) Inclusion/exclusion criteria must be stated and non-responders should be identified and excluded prior to begin the study;
(d) 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;
(e) 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;

(f) The principles of Good Veterinary Clinical Practice (GVCP) and Good Laboratory Practice (GLP) should be adhered to during the study;

(g) 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:

(a) The response can be measured precisely over a reasonable range;

(b) The response can be measured repeatedly to obtain time-course from the beginning to end of the response;

(c) It should be possible to derive the common parameters of comparison;

(d) It should be possible to derive the common parameters of comparison like Cmax, Tmax and AUC;

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

I.2 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. cross-over 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.

(a) 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);

(b) The number of animals chosen and acceptance limits should be justified.

LIST OF REFERENCES

1. ICH Q6A guidelines
2. ICH Q8 guidelines: Pharmaceutical Development
3. ICH Q9 guidelines: Quality Risk Management
4. ICH Q10 guidelines
5. VICH GL1 Text on Validation of Analytical Procedures
6. VICH GL2 Validation of Analytical Procedures: Methodology
7. Reference documents: ICH Q5A, Q5D, and Q6B
8. VICH GL39 — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Medicinal Products: Chemical Substances + Decision trees.
9. ICH Q3B, Q3C and Q6A
10. VICH GL1 Text on Validation of Analytical Procedures
11. VICH GL2 Validation of Analytical Procedures: Methodology
12. ICH Q2
13. WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials
14. VICH GL5 Photostability Testing of New Veterinary Drug Substances and Medicinal Products
15. VICH GL31 (Safety Repeat dose); Studies to evaluate the safety of residues of veterinary drugs in human food: Repeat dose toxicity testing
16. VICH GL37 (Safety: Repeat-dose chronic toxicity) Studies to evaluate the safety of residues of veterinary drugs in human food: Repeat-dose (chronic) toxicity testing
17. VICH GL6 (Ecotoxicity - Phase 1) Environmental Impact Assessment (EIAs) for veterinary medicines (VPPs) - Phase 1

LIST OF ANNEXES

Annex I: Cover Letter

Annex II: Product Registration Application Form

Annex III: Quality Overall Summary(QOS)

Annex IV: Letter of Access to CEP

Annex V: Letter of Access to APIMF

Annex VI: Quality Information Summary (QIS)

Annex VII: Presentation of Bioequivalence Trial Information

Annex VIII: Biowaiver Application Form

Annex IX: Container Labelling Format

Annex X: Information Leaflet Format

Annex XI: Prescribing Information (Summary of Product Characteristics) Format

Annex XII: Product Registration Certificate

Note: The annexes mentioned above are available on the Rwanda FDA website under the Veterinary Medicines Registration Division.

ENDORSEMENT OF THE GUIDELINES

	Prepared by	**Checked by**		**Approved by**
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