



**REGISTRATION OF VETERINARY PHARMACEUTICAL  
PRODUCTS  
GUIDELINES FOR SUBMISSION OF APPLICATIONS**

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## LIST OF ABBREVIATIONS

<b>INN</b>	International Non-proprietary Name
<b>API</b>	Active Pharmaceutical Ingredient
<b>JAN</b>	Japanese Accepted Name
<b>LOD</b>	Loss on Drying
<b>MedDRA</b>	Medical Dictionary for Drug Regulatory Authorities
<b>M.R</b>	Modified Release
<b>Mg</b>	Milligramme
<b>MI</b>	Millilitre
<b>MRA</b>	Medicines Regulatory Authority
<b>NCE</b>	New Chemical Entity
<b>NMT</b>	Not More Than
<b>PhEur</b>	European Pharmacopoeia
<b>QA</b>	Quality Assurance
<b>RH</b>	Relative Humidity
<b>SMACS</b>	Starting Materials Certification Scheme
<b>SMF</b>	Site Master File
<b>TSE</b>	Transmissible Spongiform Encephalopathy
<b>VICH</b>	Veterinary International Conference on Harmonization requirements for Registration of Veterinary Pharmaceutical product
<b>VPPs</b>	Veterinary Pharmaceutical products
<b>VMD</b>	Veterinary Medicines Directorate
<b>FPP</b>	Finished Pharmaceutical Products
<b>CTD</b>	common Technical Document
<b>LTR</b>	Local Technical Representative
<b>BP</b>	British Pharmacopoeia
<b>Ph.Eur</b>	European Pharmacopoeia
<b>JP</b>	Japanese Pharmacopoeia
<b>USP</b>	United States Pharmacopeia

<b>PSUR</b>	Periodic Safety Update Reports
<b>FIFO</b>	First in First out
<b>cGMP</b>	Compliance to the current Good Manufacturing Practices
<b>QIS</b>	Quality Information Summary
<b>APIMF</b>	Active Pharmaceutical Master File
<b>CEP</b>	European Pharmacopoeia
<b>GCP</b>	Good Clinical Practice
<b>GLP</b>	Good Laboratory Practice
<b>QOS</b>	Quality overall summary
<b>NCE</b>	New Chemical Entities
<b>FPP</b>	Finished Pharmaceutical Product
<b>AUC</b>	Area Under the plasma Concentration time curve
<b>Cmax</b>	Maximum plasma concentration
<b>PK</b>	Pharmacokinetic
<b>PD</b>	Pharmacodynamic
<b>BA</b>	Bioavailability
<b>BE</b>	Bioequivalence
<b>ODT</b>	Oral Dispersible Tablets
<b>CEP</b>	European Certificate of Suitability
<b>DMF(s)</b>	Drug Master File(s)
<b>UN</b>	United Nations Agencies
<b>INN</b>	International Non-proprietary Name
<b>USAN</b>	United States Adopted Name
<b>BAN</b>	British Approved Name
<b>CAS</b>	Chemical Abstracts Service registry number
<b>BCS</b>	Biopharmaceutics Classification System
<b>IR</b>	Infrared
<b>UV</b>	Ultraviolet
<b>NMR</b>	Nuclear Magnetic Resonance
<b>MS</b>	Mass Spectra
<b>DSC</b>	Differential Scanning Calorimetry

<b>ssNMR</b>	Solid-State Nuclear Magnetic Resonance
<b>RSD</b>	relative standard deviation
<b>CPP</b>	critical process parameters
<b>GVCP</b>	Good Veterinary Clinical Practice
<b>GLP</b>	Good Laboratory Practice

## DEFINITIONS OF TERMS

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.

**Active pharmaceutical ingredient (API)** means any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

**Applicant** means the person by, or on whose behalf, an application for, an update or amendment to an existing registration, is made. After the product is registered, the applicant shall be the "Marketing Authorisation Holder".

**Authority** means the Veterinary Medicines Directorate, or its acronym "VMD" established under Legal Notice No. 209 of 2015.

**Bioavailability** Means the rate and extent to which the active ingredient reaches the systemic circulation and becomes available to the site of action.

**Composition** in relation to a veterinary pharmaceutical product means the ingredients of which it consists, proportions, degree of strength, quality and purity in which those ingredients are contained.

**Container** means a bottle, jar, box, packet, sachet or other receptacle that contains or is to contain within it, not being a capsule or other article in which the veterinary pharmaceutical product is or is to be administered or consumed: and where any such receptacle is or is to be contained in another receptacle which includes the former but does not include the latter receptacle.

**Container labelling** means all information that appears on any part of a container, including that on any outer packaging of such as a carton.

**Pharmaceutical product** is 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 farmhouses.

**Drug Master File** Means a master file that provides a full set of data on an API In some countries, the term may also comprise data on an excipient or a component of a Veterinary product such as a container.

**Established active pharmaceutical ingredient** Means APIs which are subject of the current veterinary pharmacopoeia or those well documented in the literature and generally recognized as safe and effective for use as veterinary pharmaceutical products.

**Excipient** means any component of a finished dosage form, which has no therapeutic value.

**Expert report** means a summary and interpretation of data, with conclusions, prepared by an independent expert on the subject.

**Finished veterinary pharmaceutical product** means a veterinary product that has undergone all stages of production, including packaging in its final container and labelling.

**Formulation** means the composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

**General sale veterinary pharmaceutical product means** any veterinary pharmaceutical product whose use does not need the direction or prescription by a veterinarian recognized under the current forced regulations.

**Generic (multisource) products** means veterinary products that are pharmaceutical equivalents or alternatives to innovator or reference products and which are intended to be therapeutically equivalent and can therefore be used interchangeably with the innovator or reference product.

**Immediate release dosage form** means a dosage form that is intended to release the entire active ingredient on administration with no enhanced, delayed or extended release effect.

**Innovator pharmaceutical product** means a veterinary pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to the requirements at the time of authorization).

**Interchangeability** means an interchangeable pharmaceutical product means one that is therapeutically equivalent to an innovator (reference) product.

**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 veterinary medicine.

**Manufacture (manufacturing)** means all operations of purchase of materials and products, production, quality control, release, storage, shipment of finished veterinary products and the related controls.

**Marketing authorization (product license, registration certificate)** is a legal document issued by the competent drug regulatory Authority 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.

**Manufacturer** means a person or firm that is engaged in the manufacture of veterinary pharmaceutical product (s).

**Manufacturing site** means the location where the manufacturing process of a pharmaceutical product is undertaken.

**Manufacture** means all operations of receipt of materials, production, packaging and repackaging and labelling and re-labelling, quality control, release, storage and distribution of pharmaceutical products and related controls.

**New active pharmaceutical ingredient** means a veterinary pharmaceutical product (active ingredient), including its salts, esters, derivatives, etc. or biological agent, which is not a subject of current pharmacopoeias.

**New pharmaceutical product** means a pharmaceutical product that contains a new API, a new combination of marketed APIs or a new multisource (generic) veterinary pharmaceutical product.

**Pharmacopoeia means** a current edition of official publication containing a list of pharmaceutical products with their effects and directions for their use. E.g British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia , Japanese Pharmacopoeia etc

**Retention fee** means a fee paid annually to maintain marketing authorization.

**Specifications** is a document describing in detail the requirements with which the products or materials used or obtained during manufacture have to conform. Specifications serve as a basis for quality evaluation.

**Shelf life specifications** means the combination of physical, chemical, biological and microbiological test requirements that an active ingredient must meet up to its retest date or a drug product must meet during its shelf life.

**Release specifications** means the combination of physical, chemical, biological and microbiological test requirements that determine whether a drug product is suitable for release at the time of its manufacture.

**Starting material means** any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

**API starting material** is a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. An API starting material can be an article of commerce, a material purchased from one or more suppliers under contract or commercial agreement, or produced in-house.

**Primary batch** is a batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for establishing a re-test period or shelf life.

**Variation** means a change to any aspect of a veterinary pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

**Veterinary Pharmaceutical Product (VPP)** means any substance or combination of substances which may be administered to animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in animals.

**Therapeutic equivalence** means two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or in vitro study

**Master formula** A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

**Mock-up is** a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/ labelling of the medicine. Also referred to as a paper copy or computer generated version.

**On-going stability study** is the study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

**In-process controls are** Checks performed during production in order to monitor and if necessary to adjust the process to ensure that, the product conforms to its specifications. The control of the environment or equipment may be regarded as a part of in-process control.



**Local Technical Representative (LTR):** Any applicant who is not resident in Kenya shall appoint a local technical representative who must be a company incorporated in Kenya and authorized by the Authority to deal in pharmaceutical products and must hold a wholesale operating license. The appointment shall be notified to the Authority by submitting a letter of appointment supported by original copy of power of attorney duly notarised in country of origin, and registered with registrar of Companies in Kenya.

## INTRODUCTION

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 for approval that a veterinary pharmaceutical product is registered in Kenya. According to the CTD format. The guidelines are arranged as follows:

Table 1.1

<b>Module 1:</b>	Administrative Requirements
<b>Module 2:</b>	Overviews and summaries
<b>Module 3:</b>	The Quality Requirements for the Active Pharmaceutical Ingredients (API) and Finished Pharmaceutical Products (FPP);
<b>Module 4:</b>	Non-Clinical Study Report
<b>Module 5:</b>	Clinical Study Report

Note: Applicants should not modify the overall organization of the CTD.

### Scope

These guidelines provide guidance to the applicants on the arrangement of information to be provided to the Authority in seeking marketing authorization for pharmaceutical products for veterinary use. It also assists the Authority during the evaluation and registration processes.

### Preparation and Presentation of Information in CTD format

- i. The applicant shall prepare and present the product dossier information in CTD format according to the requirements as stipulated in these guidelines:
- ii. The application should be typed in English. Any document that is in any language other than English must be accompanied by a certified or notarized English translation.
- iii. The application must contain a complete index to the various appendices.
- iv. 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.
- v. All pages of the application should be numbered in the style: page x of y.

- vi. Payment of fees shall be made in accordance to Fifth Schedule of the regulations (LN. No. 209 of 2015)
- vii. The application should be submitted in hard and soft copies (CD-ROM or External Driver) addressed to the authority
- viii. The PDF documents should be in Optical Character Recognition, selectable and searchable
- ix. A separate application is required for each product. The following products will be regarded as either being the same product or separate product applications.

No.	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		X
4	Different pack-sizes of exactly the same strength and formulation.	X	
5	Different strengths and formulations		X
6	Uncoated and coated tablets of the same strength and formulation		X
7	Liquids/Solutions (excluding parenterals) Ointments/Creams/ different container sizes of the same strength and formulation.		X
8	The same container size of different strengths and formulations. Ampoules and Vials and Large Volume Parenterals		X
9	Ampoules or single dose vials containing identical solutions of the same strength but of different volumes (i.e. Resulting in different total doses).		X
10	Ampoules containing solutions of different strengths.		X
11	Ampoules and single dose vials containing e.g. dry powder, crystals of different mass	X	
12	Ampoules and single dose vials containing the same respective masses of e.g. Dry powder, crystals.	X	

13	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	
14	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 as fully described in dossier.	X	
15	Ampoules containing identical solutions of different volumes used only as diluents in the reconstitution of a preparation for parenteral use		X
16	Multidose vials containing different volumes of the same strength and formulation with the same dosage schedule.	X	
17	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	
18	Multidose vials containing dry powder of different mass of the reconstituted.	X	
19	An ampoule of diluents packed together with any preparation including biological medicines if diluent is fully described in Dossier.	X	
20	Infusion solutions of the different volumes and of the same formulation, which are packed in containers of exactly the same type of material depending on the relevant information, submitted.		X
21	Infusion solutions of the different volumes and of the same type of material depending on the relevant information submitted.		X
22	Infusion solutions of the same formulation and of the same or different volume, which are packed containers, made of different types of materials.		X
23	A preparation, packed in plastic containers, intended to be marketed in glass containers containing the same volume and the same formulation.		X

24	Products with the same strength and formulation but with different colours and/or flavours.		X
25	Applications containing the same API(s) applying for additional indications that render the product in a different scheduling status, or different pharmacological classification, or have any other restrictions imposed other than the original application.		X
26	Removal of antimicrobial preservative from single dose presentation of registered vaccine that included a preservative in the original approved formulation		X
27	Same formulation with different proprietary names whether of the same or different applicants		X

### 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 Pharmacopoeia (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 be validated and appropriate references cited.

## **2 SUBMISSION OF APPLICATION**

An application for product registration for either locally manufactured or imported shall be made in writing via a cover letter and application form dated and signed by the applicant. If the applicant is a foreign company, the applicant shall appoint a local technical representative through whom an application shall be submitted. The local agent shall be a registered wholesale dealer.

The application should be submitted to Authority through the authorized local technical Representative to the following address:

The Chief Executive Officer  
Veterinary Medicines Directorate  
P. O. Box 66171-00800,  
NAIROBI, KENYA  
Email: [vmd@kilimo.go.ke](mailto:vmd@kilimo.go.ke)

### **Types of applications**

For the purposes of submission to the Authority, applications are classified into four categories as follows:

#### **2.1.1. New applications for registration**

This is an application for registration of a veterinary pharmaceutical product that is intended to be placed on the Kenyan market for the first time.

- The applicant may only make a new application and he/she shall be the person who signs the declaration part of the application form.
- A new application for veterinary pharmaceutical product registration in Kenya shall include the following:
  1. Signed and dated original hard-copy of cover letter
  2. Signed and dated application form for product registration
  3. Proof of payment of registration fee at the time of submission
  4. Hard copy of the Dossier
  5. Electronic copy (CD of memory stick) of the Dossier in PDF, QOS, QIS, in MS Word
  6. Three commercial samples of the veterinary pharmaceutical products with CoA.

### **2.1.2 Applications for Renewal of Registration**

An application for renewal of veterinary pharmaceutical products shall be made to the Authority at least ninety (90) calendar days before expiration of the last registration by completion of the prescribed application form.

If an application for renewal is not made within three (3) months of grace period following the expiration of the registration validity, it shall be considered as a new application for registration.

Applications for renewal of registration shall be made by submission of the following:

1. Dully filled application form for renewal of registration.
2. Long term stability report for three commercial batches of the finished product
3. Periodic Safety Update Reports (PSUR)
4. Two commercial samples of the VPP with CoAs
5. A non-refundable application fee for renewal of registration
6. Any other requirements that the Authority may determine from time to time as informed by pharmacovigilance reports.

### **2.1.3 Application for Variation of a registered veterinary pharmaceutical product**

Any variation to a registered VPP information shall be notified in writing to the Authority through an application in the approved format.

An application for variation shall be submitted as per the requirements set out in the Guidelines for Variation of Registered Veterinary Pharmaceutical Products in force at the time of submission.

### **2.1.4. Retention of a veterinary pharmaceutical product on the register**

Every marketing authorization holder shall retain registered products in the register every year. This shall be done by completing the application form for retention of a veterinary medicine and pay annual retention fees as stipulated in the regulations (LN. No. 209 of 2015).

Applications for retention of a registered product for a particular year shall be made by 31<sup>st</sup> of December of the preceding year. Application received beyond this date will be penalized.

### **Receiving of new applications**

An application consists of electronic copies, online submission or specified hard copies where applicable. The Authority only receives the application of product registration when the

payment of prescribed registration fees is made. After receiving a product registration application, a reference number is assigned to the application and it will be used in all subsequent correspondences relating to the application.

### **Evaluation Procedures**

1. After receiving the VPP registration application, the Authority 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.
2. In case of a positive outcome during the screening, the application will be subjected for assessment according to the First in First out (FIFO) basis.
3. Priority assessment may be granted when the product is intended for treatment of rare animal disease conditions, to be used in case of animal disease outbreak and renewal of registration.
4. Two assessors to provide scientific and regulatory oversight regarding the quality, safety and efficacy of the product under assessment review a product dossier.
5. 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 Kenya. During the assessment, additional data and/or samples may be requested through an official communication letter.
  - a) Once a query has been issued to the applicant, the assessment process stops until the Authority receives a written response to the raised queries.
  - b) Further processing of the application may only be undertaken if responses to queries issued in the official communication letter contains all outstanding information requested in one submission.
  - c) Failure to comply with this condition or if the queries have been reissued for a second time and the applicant provides unsatisfactory responses, the application will be rejected.
  - d) In the event that the responses to the queries are not submitted within ninety (90) calendar days from the date they were issued, it will be considered that the



applicant has withdrawn the application unless the applicant has requested for extension of deadline.

- e) In cases of rejected applications, registration may only be considered upon submission of a new application 12 months from the date of rejection.

### **Compliance to the current Good Manufacturing Practices (cGMP)**

The GMP inspection is part of the VPP registration process.

1. The Authority will conduct inspection of the facility or use other means to verify whether the manufacturing site complies with cGMP requirements and/or guidelines before a product is registered.
2. No product shall be registered unless the facility complies with cGMP. During the assessment, assessors may highlight GMPs issues and communicate to the department that has mandate of inspection and compliance.

### **Technical and Registration Committee of the Council**

1. After dossier evaluation is done, a final dossier assessment report shall be presented to technical and registration committee before final decision is made by the Council for granting or rejecting registration of the product.
2. In the event, that there is safety, quality or efficacy issues to be resolved as per the decision of the technical committee, the application shall remain pending until the resolution of the raised issues.
3. If the applicant fails to provide the required data within ninety calendar days (90), it will be considered that applicant has withdrawn the application.
4. In cases of rejected applications, registration may only be considered upon submission of a new application 12 months from the date of rejection.

The Authority will register a 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 the Authority suspends or cancels the registration validity, a written official communication shall be made to the applicant.

### **Timelines for Registration**

1. 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 eighteen (18) months of receipt of the application.
2. Post Approval Variation and Renewal of registration; Complete applications will be processed within six (6) months of receiving the application including evaluation of documentation and consideration by a committee on product registration.
3. The applicant will be required to provide any requested additional data within ninety (90) calendar days. Additional data or query responses shall be processed within sixty (60) calendar days.

## **MODULE 1: ADMINISTRATIVE AND PRESCRIBING INFORMATION**

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

1. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume.
2. The annexes to the module should be submitted in separate volumes.
3. Official language is English as a mandatory language for all VPPs.

### **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**

1. Applicants should include a cover letter with all applications (Template attached to Annex 1).
2. A copy of the letter should be placed at the beginning of Module 1.
3. The cover letter for product registration shall be dated and signed by the applicant

### **1.3 Comprehensive table of content**

- i. Module 1: should include a comprehensive table of contents for the entire application.
- ii. The comprehensive table of contents should include a complete list of all documents provided in the application by module.
- iii. In the table of contents, the location of each document should be identified by referring to the volume numbers that contain the relevant documents and any tab identifiers. In general, the name for the tab identifier should be the name of the document

### **1.4 Application Information**

- i. An application to register a pharmaceutical product for veterinary use must be accompanied by a completed Application Form downloadable from the Authority's website (Template attached to Annex II).
- ii. The application form should be dully filled with relevant information and attachments, dated signed and stamped appropriately.

#### **1.4.1 Trade/Proprietary name**

Trade/Proprietary name means the (trade or brand) name which is unique to a particular drug and which generally identifies it. In case the product is being registered under trade name, a copy of trademark/proprietary name certificate issued by the relevant competent authority in Kenya will be submitted. However, approved/INN/generic name that are internationally recognized non-proprietary name of the product do not require the trademark/proprietary name certificate.

#### **1.4.2 Quality Information Summary (QIS)**

The Quality Information Summary (QIS) template (refer to the Annex III) shall be completed to provide a condensed summary of the key quality information for the PD and constitutes part of the submission package. The QIS provides accurate record of technical data in the PD at the time of prequalification.

The QIS is a condensed version of the QOS-PD in section 2.3 and represents the final agreed-upon key information on the API and FPP from the PD assessment (including, but not limited to, identification of the manufacturer(s), site addresses, API/FPP specifications, stability conclusions and relevant commitments).

#### **1.4.3 Product Information**

Provide copies of all package inserts, labels and any information intended for distribution with the product to the patient. All pharmaceutical preparations with potential for long-term use and self-administered injections must contain a patient information leaflet.

#### **1.4.4 Prescribing information (Summary of Product Characteristics)**

Provide copies of the proposed Summary of Product Characteristics (SmPC) aimed at veterinary practitioners. It should be written in English, should be legible, indelible and comprehensible.

#### **1.4.5 Container labelling**

The product should be labelled as prescribed in **Guidance on Format and Content of Labels for Pharmaceutical Products**.

#### **1.4.6 Product Information Leaflet/ Package Insert**

- i. Provide two (2) copies of package insert and any information intended for distribution with the product to the user.
- ii. The package insert should be in conformity with the SmPC.
- iii. It should be written in English, should be legible, indelible and comprehensible.

#### **1.4.7 Mock-ups and specimens**

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

#### **1.4.8 Information about the experts**

- i. Experts must provide detailed reports of the documents and particulars, which constitute Modules 3, 4 and 5.
- ii. The requirement for these signed Expert Reports may be met by providing: *The Quality Overall Summary, Non-clinical Overview/ Summary and Clinical Overview/ Summary in Module 2, A declaration signed by the experts in Module 1.*
- iii. Brief information on the educational background, training and occupational experience of the experts.
- iv. Experts should additionally indicate in their declarations the extent, if any of their professional or other involvement with the applicant / dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom.
- v. Reports should be based on an independent assessment of the dossier and references must be provided for any additional claims not supported by the dossier (A sample declaration form is attached to the Annex-IV)

#### **1.4.9 Certificates of Suitability to the CEP or APIMF**

An application to register a new pharmaceutical product (or vary an existing product) may refer 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.

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.

- Complete copies of the CEP (including any annexes) should be provided in Module 1.7. Procedures relating to APIMFs and CEPs are outlined in more detail in Module 3.
- 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 attached to **Annex V and Annex VI**. These letters should be included in Module 1.7.
- 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 the Authority directly by the API manufacturer when required.

#### **1.4.10 Good Manufacturing Practices (GMP)**

For all Veterinary pharmaceutical products, irrespective of the country of origin, all key manufacturing and/or processing steps in the production of active pharmaceutical ingredient, ingredients and finished pharmaceutical products must be performed in plants that comply with GMP guidelines. If available at the time of submission of application, GMP certificates from the Authority or an evidence for application for GMP inspection should be submitted in module 1.

#### **1.4.11 Good Clinical Practice (GCP) or Good Laboratory Practice (GLP)**

Provide evidence such as accredited certificate for GCP or GLP for the sites participating in the clinical studies

#### **1.4.12 Product Registration Status**

The applicant should provide a list of countries in which a similar application has been submitted, dates of submission (if available) and the status of these applications. This should detail approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case. List of the countries and certificate (s) of registration in which product has been registered should be provided.

Applicant must declare whether a marketing application of pharmaceutical product for veterinary use has been rejected prior to submission of the application in Kenya. If the pharmaceutical product for veterinary use has been rejected, repeatedly deferred, withdrawn or suspended then reasons must be stated. If rejection occurs during the evaluation process, the Authority should be informed.

#### **1.4.13 Product Samples**

Three commercial samples in the final packing size with certificate of analysis and measuring devices where applicable should be submitted at the time of application for laboratory analysis and also to enable visual inspection of the product and product package.

However, additional samples may be requested depending on tests or parameters to be carried out. Batch number, Manufacturing Date and Expiry Date should be dynamically printed on packages for all VPPs in Kenya 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.

#### **1.4.14 Certificate(s) of Suitability of the European Pharmacopoeia (CEP)**

Copy of the latest version of Certificate (s) of Suitability of the European Pharmacopoeia (CEP) (including any annexes) should be provided where applicable.

## **MODULE 2: OVERVIEWS & SUMMARIES**

### **2.1 Table of contents of Module 2:**

A table of content of module 2 should be provided

### **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.

### **2.2 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 attached to Annex VII. This should be completed for generic 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**

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;

- i. A flow diagram, as provided in 3.2.S.2.2
- ii. 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;
- iii. 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;
- iv. A description of process validation and/or evaluation, as described in 3.2.S.2.5.
- v. 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 Information on the manufacturer. A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.

- i. A flow diagram, as provided under 3.2.P.3.3.
- ii. 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.

## **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 labeling) 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 literature 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 (C<sub>max</sub>) 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
- l. Studies in juvenile animals
- i. J. The consequences of use before and during pregnancy, during lactation, and during neonatal development
- j. 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 *I 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 labeling).

## **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 summarized 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 Non-human primate
- g. Other non-rodent mammal
- h. Routes of administration should be ordered as follows
- i. Oral
- j. Intravenous
- k. Intramuscular m. Intraperitoneal
- l. Subcutaneous
- m. Inhalation
- n. Topical
- o. 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 using 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
- d. Tabulated Summary of Pharmacokinetics
- e. Written Summary of Toxicology
- f. Tabulated Summary of Toxicology

#### **2.4.1.2.1.1.2 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 brief and 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
- i. 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 brief and summarized in approximately 2 to 3 pages. This section should begin with a description of the scope of the pharmacokinetic evaluation, emphasizing, 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 summarized in this section: Absorption (extent and rate of absorption, in vivo and in-situ studies), parameters, bioequivalence and/or bioavailability (serum/plasma/ blood PK studies)

#### **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 summarized 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., renal 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

#### **2.4.1.2.1.3.1.10 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
  - i. Studies in Juvenile Animals
  - ii. Local Tolerance
  - iii. Other Toxicity Studies
- g. Discussion and Conclusions
- h. Tables and Figures (either here or included in text)

##### **2.4.1.2.1.4.2 Brief Summary**

The principal findings from the toxicology studies should be brief and 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),

##### **2.4.1.2.1.4.3 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.

##### **2.4.1.2.1.4.4 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

#### **2.4.1.2.1.4.5 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

#### **2.4.1.2.1.4.6 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

#### **2.4.1.2.1.4.7 Reproductive and Developmental Toxicity**

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

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

#### **2.4.1.2.1.4.8 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.

#### **2.4.1.2.1.4.9 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

#### **2.4.1.2.1.4.10 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.

#### **2.4.1.2.1.4.11 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.

#### **2.4.1.2.1.5. Toxicology Tabulated Summary**

##### **2.4.1.2.1.5.1. onclinical 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:

- Pharmacokinetics of FPP/VPP
- 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/VMP 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.

**2.4.1.2.5. 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.

**2.4.1.2.6. 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.

**2.4.1.2.7. 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.

- Worldwide marketing experience. The extent of the worldwide experience should be briefly discussed: any new or different safety issues identified, any regulatory actions related to safety.
- Support for the applicability to the new region of data generated in another region, where appropriate

#### **2.4.1.2.8. Benefits and Risks Conclusions**

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the bio pharmaceuticals, 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. In addition, 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:

- I. The efficacy of the *FPP/VPP* for each proposed indication.
- II. Significant safety findings and any measures that may enhance safety.
- III. Dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens.
- IV. Efficacy and safety in sub-populations, e.g., those defined by age, organ function, disease severity, and genetic polymorphisms. 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

#### **2.4.1.2.9. 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 (VMP), 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 because 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 (VMP). 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 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 pharmaceutical 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 pharmaceutical 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 optimize 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; cross-referencing to more presentations that are detailed 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 pharmaceutical product should:

- a. Identify the pharmacological class of the pharmaceutical product.
- b. Describe the particular clinical/pathophysiological condition that the pharmaceutical product is intended to treat, prevent, or diagnose (the targeted indication).
- c. Briefly summarise the scientific background that supported the investigation of the pharmaceutical product for the indication(s) that was (were) studied.
- d. Briefly describe the clinical development programme of the pharmaceutical 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, and 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). 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 because 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. 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, pharmacodynamics (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.
- b) 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).
- c) Evidence of correlations between in vitro dissolution and BA, including the effects of pH on dissolution, and conclusions regarding dissolution specifications.
- d) Comparative bioavailability, including BE conclusions, for different dosage form strengths.
- e) Comparative BA of the clinical study formulations (for clinical studies providing substantial evidence of efficacy) and the formulations to be marketed.
- f) The source and magnitude of observed inter- and intrasubject variability for each formulation in a comparative BA study.

#### **2.4.2.1.3.4 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.

#### **2.4.2.1.3.5 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**

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**

A Table of Contents should be if 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 the Authority 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

#### **3.3. S Active substance(s)**

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 CEP holder on behalf of the VMP manufacturer or applicant who refers to the CEP should duly fill out the declaration of access for the CEP.

In addition, a written commitment should be included that the applicant will inform the Authority in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP would 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.

### **3.4.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.

#### **3.5.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.

#### **3.6.~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.

#### **3.7.S.3. Analytical procedures and validation**

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

#### **3.8.S.4. Batch analysis**

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

#### **3.9.S.5. Reference standards or materials**

Information on the FPP manufacturer's reference standards.

#### **3.10. S.6. Container-closure system**

Specifications including descriptions and identification of on many packaging components.

### **3.11. 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.

### **3.12. S.1 General Information**

#### **3.12.1. 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)); and
- g) Chemical Abstracts Service (CAS) registry number.

The listed chemical names should be consistent with those appear 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.

#### **3.12.2. 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 freebase or acid should also be provided.

### 3.12.3. 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 detail.

#### *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, 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: largest dosage strength (mg) Dose/solubility volume is equal to the largest dose strength (mg) divided by 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 ( $37 \pm 0.5$  °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  $37 \pm 0.5$  °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 ( $400 \text{ mg}/1.0 \text{ mg/ml} = 400 \text{ ml}$ ).

#### *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.

#### *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*

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

### **3.13. S.2. Manufacture**

#### **3.13.1 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.

### **3.13.2. 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 simultaneously 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.

#### **3.13.3. 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, and isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be if 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.

#### **3.13.4. 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.

#### **3.13.5. S.2. 5. Process validation and/or evaluation**

Process validation and/or evaluation studies for aseptic processes and sterilization should be included.

It is expected that the manufacturing processes for all APIs be 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.

### **3.14. S.3. Characterization**

#### **3.14.1. 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**

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 pharmacopoeia! Reference standard.

##### **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.

### **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 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.

### **3.14. 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**

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  $\leq$  2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendia! 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.

### **3.16. S.4 Control of the API**

#### **3.16.1. 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 compendia 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.

### **3.16.2. 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.

### **3.16.3. 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 analyzed should be the API spiked with impurities at concentrations equivalent to their specification limits.

#### **3.16.4. 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, and date and production site of relevant API batches.

Copies of the certificates of analysis, both from the API manufacturer(s) and from 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).

#### **3.16.5. 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.

#### **3.17. 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).

### **3.18. 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-compensial 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.

### **3.19. S.7. Stability**

#### **3.19.1. 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 VMP 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 VPPs 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 VMP is placed in solution expediently, for example, under the conditions shown in the following table.

<b>STRESS FACTOR</b>	<b>CONDITIONS</b>
Heat	60°C
Humidity	75% RH or greater
Acid	0.1N HCl
Base	0.1N NaOH
Oxidative	3% H <sub>2</sub> O <sub>2</sub>
Photolytic	Metal halide, Hg Xe lamp, or UV-B/fluorescent
Metal ions (optional)	0.05 M Fe <sup>2+</sup> or Cu <sup>2+</sup>

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 to be provided.

For active substances not described in an official pharmacopoeia! Monograph, there are two options: When available, it is acceptable to provide the relevant data published in the "peer review" literature to support the proposed degradation pathways. When 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 to be provided..

*Reference: VICH GL5 Photostability Testing of New Veterinary Drug Substances and Pharmaceutical Products*

### **3.19.2. 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  $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/65\%\pm 5\%\text{RH}$  or  $30^{\circ}\text{C}\pm 2^{\circ}\text{C}/75\%\pm 5\%\text{RH}$ .

Studies covering the proposed retest period at the above mentioned long-term storage conditions would provide better assurance of the stability of APIs at the conditions of the supply chain corresponding to the Kenyan 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  $30^{\circ}\text{C}$  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)
Intermediate	30 0C ±20C	65%±5%	6
Long-term	30 0C ±20C	65%±5%.	12

### 3.19.3. 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
- 1. Reference standards or materials S.5
- J. Container closure system S.6
- k. Stability S.7.1 through S.7

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 the Authority 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.

## **3.20. P VETERINARY PHARMACEUTICAL PRODUCT(s) (VPP)(s)**

### **3.20.1. P.1 Description and Composition of the VPP**

#### **3.20.1.1 P.1.1. Description of the dosage form**

The description of the VMP 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.

#### **3.20.1.2. 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 Authority, 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 Authority, information on the diluent(s) should be provided in a separate VPP portion ("3.2.P"), as appropriate.

### **3.20.1.3. 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*

### **3.20.2. 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 VMP 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).

#### *References*

- a. *ICH Q6A guidelines*
- b. *ICH Q8 guidelines: Pharmaceutical Development*
- c. *ICH Q9 guidelines: Quality Risk Management*
- d. *ICH Q10 guidelines*

#### **3.20.2.1. P.2.1.Components of the VPP**

##### **3.20.2.1.1. 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 VMP 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.

#### **3.20.2.1.2. 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.

#### **3.20.2.2. P.2.2 Finished Pharmaceutical Product**

##### **3.20.2.2.1. 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 quadrisection 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 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  $\pm 12.5\%$  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.

#### **3.20.2.2.2. 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.

#### **3.20.2.2.3. 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.

#### **3.20.3. 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 process (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).

#### **3.20.4. 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.

#### **3.20.4. 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.

### **3.20.6. 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).

### **3.21. P.3. Manufacture**

#### **3.21.1. 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 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.

#### **3.21.2. 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).

### **3.21.3. 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 documents: ICH Q8, Q9, Q10*

#### **3.21.4. 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 documents: VICH G11, VICH GL2 ICH Q6A, Q8, Q9, Q10,*

#### **3.21.5. 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. 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;
- b. 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 Authority's inspection team; and

- c. If the process validation studies have already been conducted (e.g. For sterile products), a copy of the process validation report should be provided in the PD in lieu of (a) and (b) above.
- d. One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product largely 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 if samples taken at random will meet regulatory requirements if the confidence limits are well within compendial specifications.
- e. 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
- f. 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 Market Authorization.

The process validation protocol should include inter alia the following:

- a. 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 depyrogenating of containers, closures and equipment;
- b. Filtration of solutions;
- c. Lyophilization 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  $F_0$  range, temperature range and peak dwell time for an 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 documents: ICH Q8, Q9, Q10,*

### **3.22. P.4. Control of Excipients**

#### **3.22.1. 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. Soybean oil, peanut oil) the absence of aflatoxins or biocides should be demonstrated. The colours permitted for use are limited to those listed in the "Japanese pharmaceutical excipients", the EU "List of permitted food colours", and the FDA "Inactive ingredient guide".

For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the 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.

#### **3.22.2. P.4. 2. Analytical Procedures**

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

#### **3.22.3. 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*
3. <http://www.vichse.org/en/guidelines2.htm>

#### **3.22.4. 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 compendia! Monograph should be provided.

#### **3.22.5. 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 Module I.

*Reference documents: ICH Q5A, Q5D, Q6B,*

#### **3.22.6. P.4. 6. Novel Excipients**

For excipient(s) used for the first time in an 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.

### **3.23. P.5. Control of Veterinary Pharmaceutical Product**

#### **3.23.1. 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. "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. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities."
- b. 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.
- c. 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. PhEur,) 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  $\pm 5\%$  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.

Reference documents:

*VICH GL39 Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Medicinal Products: Chemical Substances+ Decision trees. ICH Q3B, Q3C, Q6A*

### **3.23.2. 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.

### **3.23.3. 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*

*VICH GL1 Text on Validation of Analytical Procedures*

*VICH GL2 Validation of Analytical Procedures: Methodology*

*ICHQ2 WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials*

#### **3.23.4. 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 documents: ICH Q3B, Q3C, Q6A*

#### **3.23.5. 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 documents: ICH Q3B, Q3C, Q6A*

### **3.23.6. 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 referred to for the development of specifications for VPPs.*

### **3.24. 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 documents: ICH Q6A*

### **3.25. 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.

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.

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.

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).

### **3.26. 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 pharmaceuticals (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*

Stability 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 the 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 Kenya.

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, 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 condition, 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	75±5	21

Note. Unless otherwise justified,  $30^{\circ}\text{C} \pm 2^{\circ}\text{C}/75\% \text{ RH} \pm 5\% \text{ RH}$  is the long term stability condition for products to be marketed in Kenya.

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). In addition, 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	$30 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$	12
Accelerated	$40 \pm 2^{\circ}\text{C}/\text{NMT}$	6

Note. Unless otherwise justified,  $30 \pm 2^{\circ}\text{C}$  and  $75 \pm 5\% \text{ RH}$  is the long-term stability condition products to be marketed in Kenya.

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  $40 \pm 2^{\circ}\text{C}$  and NMT  $25 \pm 5\%$  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  $30 \pm 2\text{oC}/75 \pm 5\% \text{ RH}$  (2 years) and  $40 \pm 2\text{oC}/75 \pm 5\% \text{ RH}$  (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*

#### Core Storage Statements

Testing conditions where stability has been shown	Required labelling statement	Additional labelling statement where relevant*
$30\text{oC}/75\% \text{ RH}$ (long term) $40\text{oC}/75\% \text{ RH}$ (accelerated)	Do not store above $30\text{oC}$ or store below $30\text{oC}$	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

## **3.25. R. REGIONAL INFORMATION**

### **3.25.1. R.1 Production Documentation**

#### **3.25.1.1. R.1.1 Executed Production Documents**

Executed production documents for 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 largely than that required in routine quality control. English translations of executed records should be provided where needed.

#### **3.25.1.2. 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;
- b) Dispensing, processing and packaging sections with relevant material and operational details;
- c) Relevant calculations (e.g. If the amount of API is adjusted based on the assay results or on the anhydrous basis
- d) Identification of all equipment by, at a minimum, type and working capacity  
(Including make, model and equipment number, where possible);

- e) 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));
- f) 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;
- g) Sampling plan with regard to the:
  - 1. steps at which sampling should be done (e.g. drying, lubrication and compression),
  - 11. 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),
  - 111. frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
- h) precautions necessary to ensure product quality (e.g. temperature and humidity control and maximum holding times);
- i) for sterile products, reference to standard operating procedures
- j) (SOPs) in appropriate sections and a list of all relevant SOPs at the end of the document;
- k) theoretical and actual yield;
- l) compliance with the GMP requirements.

### **3.25.2. R.2 Analytical Procedures and Validation Information**

This should be done according to the template provided in Annex VI

### **3.25.3. 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**

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.

In case of products containing new active ingredients and new combinations of active ingredients, provide full information on Non Clinical Study Reports as defined in relevant current ICH guidelines.

This chapter presents an agreed format for the organization of the nonclinical reports in the Common Technical Document for applications.

This guidance is not intended to indicate what studies are required. It merely indicates an appropriate format for the non-clinical data that have been acquired and provide references to other guidelines, which may be used for populating this format.

### **4.1. TABLE OF CONTENTS OF MODULE 4**

Table of Content of the module 4 should be provided

### **4.2. STUDY REPORT**

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 medicinal product and any dangerous effects that 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 human of residues of the veterinary pharmaceutical product or substance in food stuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of food stuff;
- c. The potential risks which may result from the exposure of human to the veterinary pharmaceutical 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 veterinary pharmaceutical 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

The study reports should be presented in the following order:

#### **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.

##### **4.2.1.2. THE 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 ED<sub>50</sub> 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.

#### **4.2.1.3. 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 pharmacodynamics interactions and mechanisms of interactions

In case of fixed dose combination or combination packs appropriate data to justify the benefit of combination against single active substance should be given.

#### **4.2.1.4. 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. Analytical Methods and Validation Reports (if separate reports are available)**

##### **4.2.1.2.2. 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.

##### **4.2.1.2.3. 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.

#### **4.2.1.2.4. Biotransformation/ Metabolism**

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.

#### **4.2.1.2.5. 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.

#### **4.2.1.2.6. 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.

#### **4.2.1.2.7. Other Pharmacokinetic Studies**

### **4.2.2. 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 formulation (product).

#### **4.2.2.1. 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.

#### **4.2.2.2. 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 veterinarians;
- c. Predict the doses that 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 veterinary pharmaceutical 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 veterinary pharmaceutical product is anticipated, for example for inhalation or dermal contact, these routes should be studied.

#### **4.2.2.3. 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 combination of active substances under examination, and to determine how these changes are related to dosage.

In the case of substances or veterinary pharmaceutical products intended solely for use in animals that 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 VPPs 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 human. 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 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.

#### *Referenece*

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

#### **4.2.2.4. Carcinogenicity (including supportive toxicokinetics evaluations)**

##### **4.2.2.4.1. 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 veterinarians 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

*Reference*

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

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

**4.2.2.4.3. Other studies**

**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 medicines 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.

*Reference*

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

**4.2.2.5. Reproductive and Developmental Toxicity**

(including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following subheadings should be modified accordingly.)

Reproductive studies will be required if there is any indication of adverse effects on potential reproduction in the preceding preclinical studies.

In the case of substances or pharmaceutical 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.

4.2.2.5.1 Fertility and early embryonic development

4.2.2.5.2 Embryo-foetal development

4.2.2.5.3 Prenatal and postnatal development, including maternal function

4.2.2.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.2.6. Local Tolerance

4.2.2.7 Other Toxicity Studies (if available)

4.2.2.7.1 Antigenicity

4.2.2.7.2 Immunotoxicity

4.2.2.7.3 Mechanistic studies (if not included elsewhere)

4.2.2.7.4 Dependence

4.2.2.7.5 Metabolites

4.2.2.7.6 Impurities

4.2.2.7.7 Other

4.2.2.7.7.1 Photosafety Evaluation

#### **4.2.2.6. 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. Anthelmintic in large animals e.g. ivermectins
- c. Expired drugs from the market
- d. Effluents from manufacturing plants

Hazardous or potentially hazardous non pharmaceutical materials (used devices e.g. needles, syringes and gloves)

(e) External preparations

#### *References*

*VICH GL6 (Ecotoxicity - Phase 1) Environmental Impact Assessment (EIAs) for veterinary medicines (VPPs) - Phase 1*

### **4.3. Literature References**

## **MODULE 5: CLINICAL STUDY REPORTS**

This module provides guidance on the organization of the study reports, other clinical data, and references within an application for registration of a pharmaceutical product. These elements should facilitate the preparation and review of a marketing application.

This module is not intended to indicate what studies are required for successful registration.

It indicates an appropriate organization for the clinical study reports that are in the application. This module recommends a specific organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as not applicable or no study conducted should be provided when no report or information is available for a section or subsection.

### **5.1. Table of Contents of Module 5**

A table of contents for study reports should be provided.

### **5.2. Tabular Listing of all Clinical Studies**

Tabular Listing of all Clinical Studies should be provided

### **5.3. 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.

## **(A) COMPARATIVE PHARMACODYNAMIC STUDIES**

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

Tabulation and graphical illustration of results and conclusion.

- I. A crossover design is preferred and where it is not appropriate, a parallel design is acceptable. The study design must consider the pathology and natural history of the condition.
- II. Studies should be done in healthy subjects or in-patient if the disease affects the actions/responses studied.
- III. Inclusion/exclusion criteria must be stated and non-responders should be identified and excluded prior to begin the study.
- IV. Measured pharmacological response should be relevant to the claimed therapeutic uses where there are more than one therapeutic use studies should be done to demonstrate the therapeutic equivalence for each use.
- V. Measurement of responses should as far as possible be quantitative, measured under double blind conditions and be recorded in an instrument producer/instrument recorded fashion. The methodology must be validated for precision, accuracy, reproducibility and specificity.
- VI. The principles of Good Veterinary Clinical Practice (GVCP) and Good
- VII. Laboratory Practice (GLP) should be adhered to during the study.
- VIII. Where possible the effect can be graphically illustrated using the area under the effect time curve, maximum effect and time of maximum effect.
- IX. 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  $C_{max}$ ,  $T_{max}$  and AUC

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

**(B) 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.

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

## LIST OF REFERENCES

- i. ICH Q6A guidelines
- ii. ICH Q8 guidelines: Pharmaceutical Development
- iii. ICH Q9 guidelines: Quality Risk Management
- iv. ICH Q10 guidelines
- v. VICH GL1 Text on Validation of Analytical Procedures
- vi. VICH GL2 Validation of Analytical Procedures: Methodology
- vii. <http://www.vichse.org/en/guidelines2.htm>
- viii. Reference documents: ICH Q5A, Q5D, Q6B,
- ix. VICH GL39 Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Pharmaceutical Products: Chemical Substances+ Decision trees.
- x. ICH Q3B, Q3C, Q6A
- xi. VICH GL1 Text on Validation of Analytical Procedures
- xii. VICH GL2 Validation of Analytical Procedures: Methodology
- xiii. ICH Q2
- xiv. WHO Guideline: Validation of analytical procedures used in the examination of medicinal materials
- xv. VICH GL5 Photostability Testing of New Veterinary Drug Substances and
- xvi. Pharmaceutical Products
- b. 16. VICH GL31 (Safety Repeat dose) ; Studies to evaluate the safety of residues of veterinary drugs in human food: Repeat dose toxicity testing
  - i. 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
  - ii. VICH GL6 (Ecotoxicity - Phase I) Environmental Impact Assessment (EIAs) for veterinary medicines (VPPs) - Phase I

# ANNEXES

**ANNEX I – COVER LETTER**

< Applicant>

< Address>

<Postal Code>

< Town>

<Country>

<Date>

<Veterinary Medicines Directorate>

< P. O. Box 66171-00800 Nairobi>

< Kenya >

Dear Sir/Madam,

**Subject: Submission of Application Dossier(s) for Marketing Authorization of <Product Name(s), [strength(s)] of active pharmaceutical ingredient(s) and dosage form(s)**

We are pleased to submit our Application Dossier(s) for a registration of veterinary medicinal products that details are as follows:

**Name of the medicinal product(s):** .....

**Pharmaceutical form(s) and strength(s):** .....

**INN/active Pharmaceutical ingredient(s):** .....

**ATC Code(s):** .....

## ANNEX I – COVER LETTER

You will find enclosed the submission dossier as specified hereafter:

Dossier  in CTD format, hard copies documents format

Proof  payment of the relevant fees for this application.

CD rd  /external driver that contains summaries in word format and body data in PDF format

We confirm  that all future submissions for this specific product will be submitted in this same format

We confirm  that the electronic submission has been checked with up-to-date and state-of-the-art antivirus software.

The submission  contains the following modules:

Module 1: Administrative information and product information

Module 2: Overviews and summaries Module 3:

Quality

Module 4: Non clinical study reports

Module 5: Clinical study reports

Type of Submission: Full Application

Abridged Application



## ANNEX I – COVER LETTER

I confirm that the Product Dossier information submitted including composition, formulation, strength, specifications and packaging is the same in all aspects as the product registered with the relevant regulatory authorities (Only for Abridged Application)

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

Yours sincerely,

<Signature>

<Name>

<Title>

<Phone number(s)>

<Email address>

## **ANNEX II: PRODUCT REGISTRATION APPLICATION FORM**

## **ANNEX III: QUALITY INFORMATION SUMMARY (QIS)**

### **FOREWORD**

The QIS template should be completed to provide a condensed summary of the key quality information for product dossiers (PDs) containing APIs of synthetic or semi-synthetic origin and their corresponding products that are filed with the Prequalification Programme.

The QIS constitutes part of the PD. The QIS provides an accurate record of technical data in the PD at the time of Marketing Authorization and thereafter serves as an official reference document during the course of GMP inspections, variation assessments and renewal of Marketing Authorizations by Kenya FDA. The QIS is a condensed version of the Quality Overall Summary – Product Dossier (QOS-PD) and represents the final, agreed upon key information from the PD review (inter alia identification of the manufacturer(s), API/FPP specifications, stability conclusions and relevant commitments).

The QIS template is structured to permit the rapid assembly of the QIS by copying requisite information from the corresponding portions of the QOS-PD filed with the original PD. It is acknowledged that the numbering of the sections may not be entirely sequential. Those sections not considered necessary to be included in the QIS have been removed (e.g. *2.3.S.5 Reference Standards or Materials*) and the remaining sections have retained their numbering to be consistent with the original PD.

For original PDs, the QIS should be provided in Word format at the time of PD submission. The QIS should be revised and submitted with the change history (see table at the end of the template) each time additional data is provided during the assessment process. If no revision is necessary due to no change in the information, a statement should be made to this effect in the covering letter. For variations and requalification dossiers, the QIS should be completed *in its entirety* (regardless of the proposed change), it should include information on *all strengths*, with any changes highlighted and it should be provided *at the time of filing*.

**When completing the QIS template, this covering *Foreword* should be deleted.**

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

<b>Summary of product information: Non-proprietary name(s) of the finished pharmaceutical product(s) (FPP)</b>	
<b>Proprietary name(s) of the finished pharmaceutical product(s) (FPP)</b>	
<b>International non-proprietary name(s) of the active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, polymorph)</b>	
<b>Applicant name and address</b>	
<b>Dosage form</b>	
<b>Application Number</b>	
<b>Strength</b>	
<b>Route of administration</b>	
<b>Proposed indication(s)</b>	
<b>Local Technical Representative (Agency)</b>	
LTR Contact person details	
<b>Local Technical Representative (LTR) contact person</b>	Surname: First Name:
<b>Physical address details</b>	
<b>Town/City</b>	
<b>Postal code</b>	
<b>Country (Within EAC)</b>	
<b>Contact person's email address</b>	
<b>Contact person's phone number</b>	
<b>FPP manufacturer Qualified Person</b>	Surname: First Name:
<b>FPP manufacturer Qualified person's contact details (including Physical address)</b>	
<b>Unit /block</b>	
<b>Road/Street</b>	
<b>Plant</b>	
<b>Village/suburb</b>	
<b>Town/City</b>	
<b>Postal code</b>	
<b>Country</b>	
<b>Contact person's email address</b>	
<b>Contact person's phone number</b>	

**ANNEX III: QUALITY INFORMATION SUMMARY (QIS)**

**(b) Administrative Summary:**

<b>Applicant's date of preparation or revision of the QIS</b>	
<b>Version and/or date of acceptance</b>	<i>( THE AUTHORITY use only)</i>

**Related dossiers (e.g. FPP(s) with the same API(s))**

<b>Reference number</b>  (eg J998)	<b>Marketing Authorization</b>  <b>granted (Y/N)</b>	<b>API, strength, dosage form</b>  (eg. Abacavir (as sulphate) 300 mg tablets)	<b>API manufacturer</b>  (including address)

**2.3.S DRUG SUBSTANCE (or ACTIVE PHARMACEUTICAL INGREDIENT (API))**

**(NAME, MANUFACTURER)**

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

**Indicate which option applies for the submission of API information:**

<b>Name of API Manufacturer:</b>	
Full details in the PD Open part DMF version number _____ Restricted part DMF version number _____ Identifier of current module 3.2.S: _____	

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

<b>Name of API manufacturer:</b>	
<input type="checkbox"/>	Full details in the PD Open part DMF version number _____ Restricted part DMF version number _____ Identifier of current module 3.2.S: _____ Option 1.
<input type="checkbox"/>	Certificate of suitability to the European Pharmacopoeia (CEP) Option 2.
<input type="checkbox"/>	Confirmation of API UN Agencies prequalification document: Option 4
<input type="checkbox"/>	Active pharmaceutical ingredient master file (APIMF) procedure: APIMF number assigned (if known): _____; version number(s) including amendments (and/or date(s)) of the open part: _____; version number(s) including amendments (and/or date(s)) of the restricted part: _____. Option 3.

**2.3.S.2 Manufacture (name, manufacturer)**

**2.3.S.2.1 Manufacturer(s) (name, manufacturer)**

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

<b>Name and address (including block(s)/unit(s))</b>	<b>Responsibility</b>	<b>API-PQ number /APIMF/CEP number (if applicable)</b>	<b>Letter of access provided?</b>

### ANNEX III: QUALITY INFORMATION SUMMARY (QIS)

#### 2.3.S.2.3 Control of Materials (name, manufacturer) – for API option 3 only

a) Name of starting material:

b) Name and manufacturing site address of starting material manufacturer(s):

#### 2.3.S.4 Control of the API (name, manufacturer)

##### 2.3.S.4.1 Specification (name, manufacturer)

API specifications of the FPP manufacturer:

Standard (e.g. Ph.Int., Ph.Eur., BP, USP, in-house)		
Specification reference number and version		
Test	Acceptance criteria	Analytical procedure (Type/Source/Version)
Description		
Identification		

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

Impurities		
Assay		
etc.		

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

**Description of the container closure system(s) for the storage and shipment of the API:**

**2.3.S.7 Stability (name, manufacturer)**

**2.3.S.7.1 Stability Summary and Conclusions (name, manufacturer)**

**Proposed storage conditions and re-test period (or shelf-life, as appropriate):**

<b>Container closure system</b>	<b>Storage statement</b>	<b>Re-test period*</b>

indicate if a shelf-life is proposed in lieu of a re-test period (e.g. in the case of labile APIs)

**2.3.P DRUG PRODUCT (or FINISHED PHARMACEUTICAL PRODUCT (FPP))**



**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

Indicate which option applies for the submission of FPP information: <check one only>

Name of API:							
Name of API manufacturer:							
<input type="checkbox"/>	Full details						
<input type="checkbox"/>	Abridged procedure						
<input type="checkbox"/>	Mutual Recognition						
<input type="checkbox"/>	EU Article 58 procedure						

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

- a) Description of the FPP:**
- b) Composition of the FPP:**

Composition, i.e. list of all components of the FPP and their amounts on a per unit basis and percentage basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)					
		Quant. per unit or per mL	%	Quant. per unit or per mL	%	Quantity per unit or per mL	%
<complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection>							
Subtotal 1							
<complete with appropriate title e.g. Film-coating >							

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)					
		Quant. per unit or per mL	%	Quant. per unit or per mL	%	Quantity per unit or per mL	%
Subtotal 2							
Total							

Composition of all components purchased as mixtures (e.g. colourants, coatings, capsule shells, imprinting inks):

**c) Description of accompanying reconstitution diluent(s), if applicable:**

***2.3.P.2.2.1 Formulation Development***

**b) Information on primary (submission, registration, exhibit) batches including comparative bioavailability or biowaiver, stability, commercial:**

**Summary of batch numbers:**

Batch number(s) of the FPPs used in

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

<b>Bioequivalence</b>	<e.g. bioequivalence batch A12345>.		
<b>Biowaiver</b>	<e.g. biowaiver batch X12345>		
<b>For proportional strength biowaiver: the bioequivalence batch of the reference strength</b>			
<b>Dissolution profile studies</b>			
<b>Stability studies (primary batches)</b>			
<packaging configuration I>			
< packaging configuration II>			
<Add/delete as many rows as necessary>			
<b>Stability studies (production batches)</b>			
< packaging configuration I>			
< packaging configuration II>			
<Add/delete as many rows as necessary>			
<b>Validation studies (primary batches)</b>			
< packaging configuration I>			
< packaging configuration II>			
<Add/delete as many rows as necessary>			
<b>Validation studies (at least the first three consecutive production batches) version(s) for process validation protocol(s)</b>			

<b>Component and quality standard (e.g. NF, BP, Ph.Eur, in-house)</b>	<b>Relevant batches</b>							
	<b>Comparative bioavailability or biowaiver</b>		<b>Stability</b>		<b>Process validation</b>		<b>Commercial (2.3.P.1)</b>	
	<b>&lt;Batch nos. and sizes&gt;</b>		<b>&lt;Batch nos. and sizes&gt;</b>		<b>&lt;Batch nos. and sizes&gt;</b>		<b>&lt;Batch nos. and sizes&gt;</b>	
	<b>Theor. quantity per batch</b>	<b>%</b>	<b>Theor. quantity per batch</b>	<b>%</b>	<b>Theor. quantity per batch</b>	<b>%</b>	<b>Theor. quantity per batch</b>	<b>%</b>
<complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection>								

**ANNEX III: QUALITY INFORMATION SUMMARY (QIS)**

Component and quality standard (e.g. NF, BP, Ph.Eur, in-house)	Relevant batches							
	Comparative bioavailability or biowaiver		Stability		Process validation		Commercial (2.3.P.1)	
	<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>	
	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%
Subtotal 1								
<complete with appropriate title e.g. Film-coating >								
Subtotal 2								
Total								

**2.3.P.3 Manufacture**

**2.3.P.3.1 Manufacturer(s) Name and address**

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

**Responsibility**

**(include block(s)/unit(s))**

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

*2.3.P.3.2 Batch Formula*

<b>Strength (label claim)</b>			
<b>Master production document</b>			
<b>Reference number and/or version</b>			
<b>Proposed commercial batch size(s) (e.g. number of dosage units)</b>			
<b>Component and quality standard</b>	<b>Quantity per</b>	<b>Quantity per</b>	<b>Quantity per</b>
<b>(and grade, if applicable)</b>	<b>batch (e.g. kg/batch)</b>	<b>batch (e.g. kg/batch)</b>	<b>batch (e.g. kg/batch)</b>
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>			
Subtotal 1			

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

<b>Strength (label claim)</b>			
<b>Master production document reference number and/or version</b>			
<b>Proposed commercial batch size(s) (e.g. number of dosage units)</b>			
<b>Component and quality standard  (and grade, if applicable)</b>	<b>Quantity per batch (e.g.  kg/batch)</b>	<b>Quantity per batch (e.g.  kg/batch)</b>	<b>Quantity per batch (e.g.  kg/batch)</b>
Subtotal 2			
Total			

**ANNEX III: OUALITY INFORMATION SUMMARY (OIS)**

***2.3.P.3.3 Description of Manufacturing Process and Process Controls***

- a) Flow diagram of the manufacturing process:
  
- b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:

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

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

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

Proposed/validated holding periods for intermediates (including bulk product):

***2.3.P.3.5 Process Validation and/or Evaluation***

- a) Summary of the process validation and/or evaluation studies conducted and/or a summary of the proposed validation protocol for the critical steps or critical assays used in the manufacturing process (e.g. protocol number, parameters, results):

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

Document code(s) for the process validation protocol(s) and/or report(s) (including reference number/version/date):

**2.3.P.5 Control of VPP**

**2.3.P.5.1 Specification(s)**

**a) Specification(s) for the FPP:**

<b>Standard (e.g. Ph.Int., BP, USP, in-house)</b>			
<b>Specification reference number and version</b>			
<b>Test</b>	<b>Acceptance criteria (release)</b>	<b>Acceptance criteria (shelf-life)</b>	<b>Analytical procedure (type/source/version)</b>
Description			
Identification			
Impurities			
Assay			
etc			



**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

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

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

<b>Description (including materials of construction)</b>	<b>Strength</b>	<b>Unit count or fill size (e.g. 60s, 100s etc.)</b>	<b>Container size (e.g. 5 ml, 100 ml etc.)</b>

**2.3.P.8 Stability**

**c) Proposed storage statement and shelf-life (and in-use storage conditions and in-use**

***2.3.P.8.1 Stability Summary and Conclusions***

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

period, if applicable):

Container closure system	Storage statement	Shelf-life

**2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment**

(a) Stability protocol for *Primary stability batches* (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch number(s) / batch size(s)	<primary batches>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

(b) Stability protocol for *Commitment batches* (e.g. storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch number(s) / batch size(s)	<i>&lt;not less than three production batches in each container closure system&gt;</i>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing Frequency		
Container Closure System(s)		

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

(c) Stability protocol for *Ongoing Batches* (e.g. storage conditions (including tolerances), number of batches per strength and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch size(s), annual allocation	<i>&lt;at least one production batch per year (unless none is produced that year) in each container closure system &gt;</i>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

## **ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

### ***2.3.P.8.3 Stability Data***

- (a) **Bracketing and matrixing design for commitment and/or continuing (i.e. ongoing) batches, if applicable:**

#### **WRITTEN COMMITMENTS OF THE MANUFACTURER – Kenya FDA use API**

##### **If applicable (primary stability study commitment):**

The Applicant (or API manufacturer) undertook in writing (date of letter of commitment) to continue long-term testing of <INN of API> for a period of time sufficient to cover the whole provisional re-test period (period ending month/year) and to report any significant changes or out-of-specification results immediately to Kenya FDA for the following batches:

<Batch numbers, manufacturing dates, batch size, primary packing materials>

##### **If applicable (commitment stability studies):**

Since stability data on three production scale batches were not provided with the application, the remaining number of production scale batches should be put on long-term stability testing. Any

### **ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

significant changes or out-of-specification results should be reported immediately to Kenya FDA. The approved stability protocol should be used for commitment batches.

#### **API option 1 - full details in the PD (ongoing stability study commitment)**

The Applicant undertook in writing (date of letter of commitment) a commitment regarding ongoing stability studies. Unless otherwise justified, at least one batch per year of the product will be included in the stability programme (unless none is produced during that year). The stability protocol will be that which was approved for primary batches (or the protocol was submitted for assessment). Out-of-specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend should be reported immediately to Kenya FDA. The possible impact on batches on the market should be considered in consultation with Kenya FDA inspectors.

#### **API option 2 - CEP**

The Applicant provided a commitment in writing (date of letter of commitment) to inform Kenya FDA in the event that the CEP is withdrawn. Note that withdrawal will require additional consideration of the API data requirements to support the dossier.

#### **FPP**

##### **If applicable (primary stability study commitment):**

The Applicant undertook in writing (date of letter of commitment) to continue long-term testing of < FPP reference number, trade name (INN of API), strength, pharmaceutical form> for a period of time sufficient to cover the whole provisional shelf-life (period ending month/year) and to report any out-of-specification results or significant changes immediately to Kenya FDA for the following batches: <Batch numbers, manufacturing dates, batch size, primary packing

### **ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

materials >

#### **If applicable (commitment stability studies):**

Since stability data on three production scale batches was not provided with the application, the Applicant undertook in writing, (date of letter of commitment) to put the remaining number <e.g.

additional two (2)> production scale batches of < FPP reference number, trade name (INN of API), strength, pharmaceutical form, primary packing material> on long-term stability testing. Any out-of-specification results or significant changes during the study should immediately be reported to THE AUTHORITY. The approved stability protocol should be used for commitment batches.

#### **If applicable (when the proposed largest commercial batch size is 200 000 units (x units) or less)**

The Applicant undertook in writing (date of letter of commitment) to place the first three batches of any production size larger than x units on stability. The stability protocol will be that which was approved for primary batches (or the protocol was submitted for assessment). Out-of- specification results or significant atypical trends will be investigated. Any confirmed significant change, out-of-specification result, or significant atypical trend will be reported immediately to THE AUTHORITY.

#### **Ongoing stability study commitment**

The Applicant undertook in writing (date of letter of commitment) a commitment regarding ongoing stability studies. Unless otherwise justified, at least one batch per year of the product manufactured in every primary packaging type will be included in the stability programme

**ANNEX III: QUALITY INFORMATION SUMMARY (OIS)**

(unless none is produced during that year). The stability protocol will be that which was approved for primary batches (or the protocol was submitted for assessment). Out-of- specification results or significant atypical trends should be investigated. Any confirmed significant change, out-of- specification result, or significant atypical trend should be reported immediately to THE AUTHORITY. The possible impact on batches on the market should be considered in consultation with Kenya THE AUTHORITY inspectors.

**If applicable (validation of production batches)**

Validation data on production scale batches of not less than three (3) consecutive batches of < FPP reference number, trade name (INN of API), strength, pharmaceutical form, primary packing material > was not provided with the application. Therefore, the Applicant submitted a written commitment (date of letter of commitment) that three consecutive production batches would be prospectively validated and a validation report—in accordance with the details of the validation protocol provided in the dossier— would be made available as soon as possible for evaluation by assessors or for verification by the THE AUTHORITY inspection team.

**Change History**

**Date of preparation of original QIS:**

<b>Date of revised version</b>	<b>Section (e.g. S.2.1)</b>	<b>Revision</b>



**ANNEX IV: Letter of Access to CEP**

<Applicant>  
<Address>  
<Address>  
<Post code> <Town>  
<Country  
<Date>

Veterinary Medicines Directorate

P. O. Box 66171-00800

Nairobi, Kenya

Dear Sir/Madam,

**Subject: Authorization to access Certificate of Suitability (CEP)**

Reference is made to the above subject matter.

Consent is hereby granted to THE AUTHORITY to make reference to this company's Certificate(s) of Suitability (CEPs) [*number(s)*] for [*API(s) name(s)*] in the evaluation of applications relating to the registration of [*medicine name(s)*] submitted to THE AUTHORITY by (*applicant's name*).

This consent does/does not\*\* include authorization to supply information or extracts from or the whole of the data to:

(Name of company or individual) The

API is manufactured by:

**ANNEX IV: Letter of Access to CEP**

*(Names and addresses of all manufacturing sites and manufacturing steps carried out at site)*

A formal agreement exists between the applicant of the medicine and the manufacturer of the API, which ensures that information will be communicated between them. Except as permitted by THE AUTHORITY guidelines relating to changes to medicines, such changes will not be made to the API to be used in manufacture of the medicine destined to be distributed in Kenya before written approval is granted by the THE AUTHORITY.

In addition, we commit that we will inform THE AUTHORITY in the event that the CEP is withdrawn.

I understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines.

Any questions arising from THE AUTHORITY evaluation of this CEP should be forwarded to:

*(Name and address)*

Yours faithfully

{Signature of Company Representative}

{Name}

{Position in Company}

{Date}

**ANNEX V: LETTER OF ACCESS TO APIMF**

<Applicant>  
<Address>  
<Address>  
<Post code> <Town>  
<Country  
<Date>

Veterinary Medicines Directorate

P. O. Box 66171-00800

Nairobi, Kenya

Dear Sir/Madam,

**Subject: Authorization to access Active Pharmaceutical Ingredient Master File**

Reference is made to the above subject matter.

Consent is hereby granted to THE AUTHORITY to make reference to this company's Active Pharmaceutical Ingredient Master File(s) for [API(s) name] in the evaluation of applications relating to the registration of [medicine name(s)] submitted to THE AUTHORITY by the (applicant's name).

This consent does/does not include authorization to supply information or extracts from or the whole of the data to:

(Name of company or individual)

## ANNEX VI: QUALITY OVERALL SUMMARY(QOS)

The substance is manufactured by:

(Names and addresses of all manufacturing sites and manufacturing steps carried out at site)

A copy of the *applicant's Part of the APIMF* as specified in the Active Pharmaceutical Ingredient Master File Procedure has been supplied to the applicant.

A formal agreement exists between the applicant of the medicine and the manufacturer of the API, which ensures that information will be communicated between them and to THE AUTHORITY before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except as permitted by the THE AUTHORITY guidelines relating to changes to medicines, such changes will not be made to the API to be used in manufacture of the medicine destined to be distributed in Kenya before written approval is granted by the THE AUTHORITY.

I understand that the consequences of failure to obtain approval for changes where approval is necessary may include de-registration and recall of batches of medicines.

This APIMF (or data identical to that contained therein) has also been submitted to and approved by the regulatory authorities in (*list of countries with stringent regulatory systems*), and THE AUTHORITY is authorized to request and refer to the evaluation reports of these agencies.

THE AUTHORITY is also authorized to exchange its own evaluation reports with these and other regulatory authorities.

Any questions arising from THE AUTHORITY's evaluation of this APIMF should be forwarded to:

{Name and address }

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

Yours faithfully

{Signature of Company Representative}

{Name}

{Position in Company}

{Date}

## **ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

### **General Instructions**

**Quality overall summary (QOS) template** should be completed for pharmaceutical products containing active substances of synthetic or semisynthetic origin and their corresponding VPPs.

All sections and fields in the QOS template that would be applicable should be completed.

It is understood that certain sections and fields may not apply and should be indicated as such by reporting –not applicable in the appropriate area with an accompanying explanatory note.

The use of tables to summarize the information is encouraged, where possible. The tables included in the template may need to be expanded or duplicated (e.g. for multiple strengths), as necessary.

These tables are included as illustrative examples of how to summarize information. Other approaches to summarize the information can be used if they fulfill the same purpose.

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

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

Should you have any questions regarding this form, please contact **THE AUTHORITY**

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

**(a) Summary of product information:**

Non-proprietary product name of the VPP			
Proprietary name of the VPP			
International non-proprietary name(s) of the active pharmaceutical ingredient(s) (API(s)), including for (salt, hydrate, polymorph)			
Applicant name and address			
Dosage form			
Reference Number(s)			
Strength(s)			
Route of administration			
Proposed indication(s)			
Contact information	Name: Phone: Fax: Email:		

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

**ACTIVE PHARMACEUTICAL INGREDIENT (API)**

Complete the following table for the option that applies for the submission of API information:

Name of API:	
Name of API manufacturer:	
<input type="checkbox"/>	<p>Full details in the PD:</p> <ul style="list-style-type: none"> <li>•Summaries of the full information should be provided under the appropriate sections; see Section 3.2.S in the Quality guideline.</li> </ul>
<input type="checkbox"/>	<p>Certificate of suitability to the European Pharmacopoeia (CEP):</p> <p>is a written commitment provided that the applicant will inform THE AUTHORITY in the event that the CEP is withdrawn and has acknowledged that withdrawal?</p>
	<p>of the CEP will require additional consideration of the API data requirements to support the dossier:</p> <p><input type="checkbox"/> yes, <input type="checkbox"/> no;</p> <p>a copy of the most current CEP (with annexes) and written commitment should be provided in <i>Module 1</i>;</p> <p>the declaration of access should be filled out by the CEP holder on behalf of the FP manufacturer or applicant to THE AUTHORITY who refers to the CEP; and</p> <p>summaries of the relevant information should be provided under the appropriate section (e.g. S.1.3, S.3.1, S.4.1 through S.4.4, S.6 and S.7; see Quality guideline).</p>
<input type="checkbox"/>	<p>Active pharmaceutical ingredient master file (APIMF):</p> <p>A copy of the letter of access should be provided in <i>Module 1</i>; and summaries of the relevant information from the Open part should be provided under the appropriate section see Section 3.2.S in the Quality guideline</p>



## **ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

### **2.3.S.1 General Information**

#### *2.3.S.1.1 Nomenclature*

- (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, USAN, BAN):
- (f) Chemical Abstracts Service (CAS) registry number:

#### *2.3.S.1.2 Structure*

- (a) Structural formula, including relative and absolute stereochemistry:
- (b) Molecular formula:
- (c) Relative molecular mass:

#### *2.3.S.1.3 General Properties*

- (a) Physical description (e.g. appearance, colour, physical state):
- (b) Solubilities:

In common solvents:

## ANNEX VI: QUALITY OVERALL SUMMARY(QOS)

Quantitative aqueous pH solubility profile (pH 1 to 6.8) at 37°C:

Medium (e.g. pH 4.5 buffer)	Solubility (mg/ml)
pH 1.2	
pH 4.5	
pH 6.8	

Dose/solubility volume calculation:

(c) Physical form (e.g. polymorphic form(s), solvate, hydrate):

Polymorphic form:

Solvate: Hydrate:

(d) Other:

Property	
pH	
pK	
Partition coefficients	
Melting/boiling points	
Specific optical rotation (specify solvent)	
Refractive index (liquids)	
Hygroscopicity	

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

UV absorption maxima/mol absorptivity	
Other	

**2.3.S.2 Manufacture***2.3.S.2.1 Manufacturer(s)*

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

<b>Name and address (including block(s)/unit(s))</b>	<b>Responsibility</b>	<b>APIMF/CEP number (applicable)</b>

- (b) Manufacturing authorization for the production of API(s) and, where available, certificate of GMP compliance (GMP information should be provided in *Module 1*):

***2.3.S.2.2 Description of Manufacturing Process and Process Controls***

- (a) Flow diagram of the synthesis process(es):
- (b) Brief narrative description of the manufacturing process(es):

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

(c) Alternate processes and explanation of their use:

(d) Reprocessing steps and justification:

**2.3.S.2.3 Control of Materials**

(a) Summary of the quality and controls of the starting materials used in the manufacture of the API:

<b>Step/starting material</b>	<b>Test(s)/method(s)</b>	<b>Acceptance criteria</b>

(b) Name and manufacturing site address of starting material manufacturer(s):

(c) Where the API(s) and the starting materials and reagents used to manufacture the API(s) are *without* risk of transmitting agents of animal spongiform encephalopathies, a letter of attestation confirming this can be found in:

**2.3.S.2.4 Controls of Critical Steps and Intermediates**

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

<b>Step/materials</b>	<b>Test(s)/method(s)</b>	<b>Acceptance criteria</b>

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**


***2.3.S.2.5 Process Validation and/or Evaluation***

(e) Description of process validation and/or evaluation studies (e.g. for aseptic processing and sterilization):

***2.3.S.2.6 Manufacturing Process Development***

(f) Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or bio-waiver, stability, scale-up, pilot and, if available, production scale batches:

**2.3.S.3 Characterisation*****2.3.S.3.1 Elucidation of Structure and other Characteristics***

(a) List of studies performed (e.g. IR, UV, NMR, MS, elemental analysis) and conclusion from the studies (e.g. whether results support the proposed structure):

(b) Discussion on the potential for isomerism and identification of stereochemistry (e.g. geometric isomerism, number of chiral centres and configurations) of the API batch(es) used in comparative bioavailability or biowaiver studies:

(c) Summary of studies performed to identify potential polymorphic forms (including solvates):

(d) Summary of studies performed to identify the particle size distribution of the API:

## ANNEX VI: QUALITY OVERALL SUMMARY(QOS)

(e) Other characteristics:

### 2.3.S.3.2 Impurities

(a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:

i. List of API-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure and origin:

API-related (chemical descriptor)	impurity name	Structure	Origin

(ii) List of process-related impurities (e.g. residual solvents, reagents), including compound names and step used in synthesis:

Process-related impurity (compound name)	Step used in synthesis

(a) Basis for setting the acceptance criteria for impurities:

i. Maximum daily dose (i.e. the amount of API administered per day) for the API,

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

corresponding to VICH Reporting/Identification/Qualification

Thresholds for the API-related impurities and the concentration limits (ppm) for the process-related impurities (e.g. residual solvents):

<b>Maximum daily dose for the API:</b>	<x mg/day>		
<b>Test</b>	<b>Parameter</b>	<b>VICH</b>	<b>threshold</b>
		<b>0</b>	<b>concentration limit</b>
API-related impurities	Reporting Threshold		
	Identification Threshold		
	Qualification Threshold		
Process-related impurities	<solvent 1>		
	<solvent 2>, etc.		

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

(ii) Data on observed impurities for relevant batches (e.g. comparative bioavailability or biowaiver, stability batches):

Impurity (API-related and process-related)	Acceptance Criteria	Results (include batch number* and use**)		

\*include strength, if reporting impurity levels found in the FPP (e.g. for comparative studies)

\*\*e.g. comparative bioavailability or bio-waiver studies, stability

(iii) Justification of proposed acceptance criteria for impurities:

**2.3.S.4 Control of the API**

*2.3.S.4.1 Specification*

(a) API specifications of the FPP manufacturer:

Standard (e.g. Ph.Int., Ph.Eur., BP, USP, House)		
Specification reference number and version		
Test	Acceptance criteria	Analytical procedure (Type/Source/Version)
Description		
Identification		
Impurities		
Assay		
etc.		



## ANNEX VI: QUALITY OVERALL SUMMARY(QOS)

### 2.3.S.4.2 Analytical Procedures

Summary of the analytical procedures (e.g. key method parameters, conditions, system suitability testing):

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

- (a) Summary of the validation information (e.g. validation parameters and results for non-compensia methods):
- (b) Summary of verification information on compensia methods

#### 2.3.S.4.4 Batch Analyses

- (a) Description of the batches:

Batch number	Batch size	Date and site of production	Use (e.g. comparative bioavailability or biowaive stability)

- (b) Summary of batch analyses release results of the FPP manufacturer for relevant batches (e.g. comparative bioavailability or bio-waiver, stability):

Results	Criteria			
		<batch x>	<batch y>	etc.
Description				
Identification				
Impurities				
Assay				
etc.				

- (c) Summary of analytical procedures and validation information for those

## ANNEX VI: QUALITY OVERALL SUMMARY(QOS)

procedures not previously summarized in 2.3.S.4.2 and 2.3.S.4.3 (e.g. historical analytical procedures):

### 2.3.S.4.5 Justification of Specification

Justification of the API specification (e.g. evolution of tests, analytical procedures and acceptance criteria, differences from officially recognized compendial standard(s)):

### 2.3.S.5 Reference Standards or Materials

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

### 2.3.S.6 Container Closure System

- (a) Description of the container closure system(s) for the shipment and storage of the API (including the identity of materials of construction of each primary packaging component and a brief summary of the specifications):

Packaging component	Materials of construction	Specifications (list parameters e. identification (IR))

- (b) Other information on the container closure system(s) (e.g. suitability studies):

### 2.3.S.7 Stability

#### 2.3.S.7.1 Stability Summary and Conclusions

- (a) Summary of stress testing (e.g. heat, humidity, oxidation, photolysis, and acid/base): and

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

results:

<b>Stress condition</b>	<b>Treatment</b>	<b>Results (e.g. including discussion whether mass balance is observed)</b>
Heat		
Humidity		
Oxidation		
Photolysis		
Acid		
Base		
Other		

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

<b>Storage condition (°C, % RH)</b>	<b>Batch number</b>	<b>Batch size</b>	<b>Container system</b>	<b>closure</b>	<b>Completed proposed) intervals</b>	<b>(an testin</b>

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

Summary of the stability results observed for the above accelerated and long-term studies:

Test	Results
Description	
Moisture	
Impurities	
Assay	
etc.	

(b) Proposed storage statement and re-test period (or shelf-life, as appropriate):

Container closure system	Storage statement	Re-test period*

\* Indicate if a shelf-life is proposed in lieu of a re-test period (e.g. in the case of labile APIs)

**2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment**

(a) Stability protocol for *Primary stability batches* (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch number(s) / batch size(s)		
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

(b) Stability protocol for *Commitment batches* (e.g. storage conditions (including tolerances),

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch number(s) / batch size(s)	<not less than three production batches>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

(c) Stability protocol for Ongoing batches (e.g. storage conditions (including tolerances), batch sizes and annual allocation, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Annual allocation	<at least one production batch per year (unless none produced that year)in each container closure system >	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	

## ANNEX VI: QUALITY OVERALL SUMMARY(QOS)

Parameter	Details	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

### 2.3.S.7.3 Stability Data

- (a) The actual stability results should be provided in *Module 3*.
- (b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4 (e.g. analytical procedures used only for stability studies):

## 2.3.P VETERINARY MEDICINAL PRODUCT (VPP)

### 2.3.P.1 Description and Composition of the VPP

- (a) Description of the VPP:
- (b) Composition of the VPP:
- (c) Composition, i.e. list of all components of the VPP and their amounts on a per unit basis and percentage basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any):

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

Component quality standard (a grade, if applicable)	Function	Strength (label claim)					
		Quant. unit	p%	Quant. unit	p%	Quantity unit	p%
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>							
Subtotal 1							
<complete with appropriate title e.g. Film-coating >							
Subtotal 2							
Total							

(a) Composition of all *components purchased as mixtures* (e.g. colourants, coatings, capsule shells, imprinting inks):

(b) Description of accompanying reconstitution diluent(s), if applicable:

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

**2.3.P.2 Pharmaceutical Development**

*2.3.P.2.1 Components of the VPP*

*2.3.P.2.1.1 Active Pharmaceutical Ingredient*

(a) Discussion of the:

- I. compatibility of the API(s) with excipients listed in 2.3.P.1:
- II. key physicochemical characteristics (e.g. water content,
- III. solubility, particle size distribution, polymorphic or solid state form) of the API(s) that can influence the performance of the FPP:

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

IV. for fixed-dose combinations, compatibility of APIs with each other:

**2.3.P.2.1.2 Excipients**

- (a) Discussion of the choice of excipients listed in 2.3.P.1 (e.g. their concentrations, their characteristics that can influence the FPP performance):

**2.3.P.2.2 Veterinary medicinal Product**

*2.3.P.2.2.1 Formulation Development*

- (a) Summary describing the development of the VPP (e.g. route of administration, usage, optimization of the formulation, etc.):
- (b) Information on primary (submission, registration, exhibit) batches including comparative bioavailability or bio-waiver, stability, commercial:

I. Summary of batch numbers:

<b>Batch number(s) of the VPPs used in</b>	
<b>Bioequivalence or biowaiver</b>	
<b>Dissolution profile studies</b>	

<b>Stability studies (primary batches)</b>			
⟨packaging configuration I⟩			
⟨ packaging configuration II⟩			
⟨Add/delete as many rows as necessary⟩			
<b>Stability studies (production batches)</b>			
⟨ packaging configuration I⟩			
⟨ packaging configuration II⟩			
(Add/delete as many rows as necessary)			
<b>Validation studies (primary batches) if available</b>			
⟨ packaging configuration I⟩			
⟨ packaging configuration II⟩			
(Add/delete as many rows as necessary)			
<b>Validation studies (at least the first thr consecutive production batches) or code(s)/version(s) for process validati protocol(s)</b>			



**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

ii Summary of formulations and discussion of any differences:

Component quality standard (e.g. NF, B Ph.Eur, in-house)	Relevant Batches							
	Comparative Bioavailability		Stability		Process Validation		Commercial 2.3P.1	
Ph.Eur, in-house	or biowaiver							
	<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>	
	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>								
Subtotal 1								
<complete with appropriate title e.g. Film-coating >								
Subtotal 2								

(a) Description of batches used in the comparative in vitro studies (e.g. dissolution) and in the in vivo studies (e.g. comparative bioavailability or biowaiver), including strength, batch number, type of study and reference to the data (volume, page):

## **ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

- (b) Summary of results for comparative in vitro studies (e.g. dissolution)
- (c) Summary of any information on in vitro-in vivo correlation (IVIVC) studies (with cross-reference to the studies in Module 5):
- (d) For scored tablets, provide the rationale/justification for scoring:

### ***2.3.P.2.2.2 Overages***

- (a) Justification of overages in the formulation(s) described in 2.3.P.1:

### ***2.3.P.2.2.3 Physicochemical and Biological Properties***

- (a) Discussion of the parameters relevant to the performance of the FPP

(e.g. pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):

### ***2.3.P.2.3 Manufacturing Process Development***

- (a) Discussion of the development of the manufacturing process of the VPP(e.g. optimization of the process, selection of the method of sterilization):
- (b) Discussion of the differences in the manufacturing process(es) for the batches used in the comparative bioavailability or biowaiver studies and the process described in 2.3.P.3.3:

### ***2.3.P.2.4 Container Closure System***

- (a) Discussion of the suitability of the container closure system (described in 2.3.P.7) used for the storage, transportation (shipping) and use of the VPPV (e.g. choice of materials, protection from moisture and light, compatibility of the materials with the VPP):
- (b) For a device accompanying a multi-dose container, a summary of the study results demonstrating the reproducibility of the device (e.g. consistent delivery of the intended volume):

### ***2.3.P.2.5 Microbiological Attributes***

- (a) Discussion of microbiological attributes of the VPP (e.g. preservative effectiveness studies):

### ***2.3.P.2.6 Compatibility***

- (a) Discussion of the compatibility of the VPP (e.g. with reconstitution diluent(s) or dosage devices, co-administered VPPs):

## **2.3.P.3 Manufacture**

### ***2.3.P.3.1 Manufacturer(s)***

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

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

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

**2.3.P.3.2 Batch Formula**

(a) List of all components of the VPP to be used in the manufacturing process and their amounts on a per batch basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Strength (label claim)			
Master production document reference number and/or version			
Proposed commercial batch size(s) (e. number of dosage units)			
Component and quality Standard (and grade, if applicable)	Quantity batch (kg/batch)	pQuantity (e batch kg/batch)	pQuantity (e batch kg/batch) p (e
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>			
Subtotal 1			
<complete with appropriate title e.g. Film-coating>			
Subtotal 2			
Total			

**2.3.P.3.3 Description of Manufacturing Process and Process Controls**

(a) Flow diagram of the manufacturing process:

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

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

(c) Justification of reprocessing of materials:

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

<b>Step</b> (e.g. granulation, compression, coating)	<b>Controls</b>

***2.3.P.3.5 Process Validation and/or Evaluation***

a) Summary of the process validation and/or evaluation studies conducted (including product quality review(s) where relevant) and/or a summary of the proposed process validation protocol for the critical steps or critical assays used in the manufacturing process (e.g. protocol number, parameters, results):

**2.3.P.4 Control of Excipients**

***2.3.P.4.1 Specifications***

(a) Summary of the specifications for officially recognized compendial excipients which include supplementary tests not included in the officially recognized compendial monograph(s):

***2.3.P.4.2 Analytical Procedures***

(a) Summary of the analytical procedures for supplementary tests:

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

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

***2.3.P.4.4 Justification of Specifications***

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

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

**2.3.P.4.5 Excipients of Human or Animal Origin**

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

**2.3.P.4.6 Novel Excipients**

For excipient(s) used for the first time in an VPP or by a new route of administration, full details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical and/or clinical), should be provided according to the API and/or VPP format

**2.3.P.5 Control of VPP**

**2.3.P.5.1 Specification(s)**

Specification(s) for the VPP:

Standard (e.g. Ph.Int., BP, USP, House)			
Specification reference number and version			
Test	Acceptance criteria (release)	Acceptance criteria (shelf-life)	Analytical procedure (type/source/version)
Description			
Identification			
Impurities			
Assay			
etc.			

**2.3.P.5.2 Analytical Procedures**

- (a) Summary of the analytical procedures (e.g. key method parameters, conditions, system suitability testing):

## ANNEX VI: QUALITY OVERALL SUMMARY(QOS)

### 2.3.P.5.3 Validation of Analytical Procedures

(a) Summary of the validation information (e.g. validation parameters and results):

### 2.3.P.5.4 Batch Analyses

(a) Description of the batches:

Strength and batch number	Batch size	Date and site of production	Use (e.g. comparative bioavailability or biowaive stability)

(a) Summary of batch analyses release results for relevant batches (e.g. comparative bioavailability or biowaiver, stability):

Test	Acceptance criteria	Results		
		<batch x>	<batch y>	etc.
Description				
Identification				
Impurities				
Assay				
etc.				

(a) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.5.2 and 2.3.P.5.3 (e.g. historical analytical procedures):

### 2.3.P.5.5 Characterisation of Impurities

(a) Identification of potential and actual impurities:

Degradation (chemical descriptor)	prod name	Structure	Origin

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

<b>Process-related impurity (compound name)</b>	<b>Step used in the FPP manufacturing process</b>

(a) Basis for setting the acceptance criteria for impurities:

i. Maximum daily dose (i.e. the amount of API administered per day) for the API, corresponding VICH Reporting/Identification/Qualification Thresholds for the degradation products in the VPP and the concentration limits (ppm) for the process-related impurities (e.g. residual solvents):

<b>Maximum daily dose for the API:</b>	<b>&lt;x mg/day&gt;</b>		
<b>Test</b>	<b>Parameter</b>	<b>VICH threshold concentration limit</b>	<b>o</b>
Degradation product	Reporting Threshold		
	Identification Threshold		
	Qualification Threshold		
Process-related impurities	<solvent 1>		
	<solvent 2>, etc.		

(ii) Data on observed impurities for relevant batches (e.g. comparative bioavailability or biowaiver):

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

Impurity (degradation prod and process-related)	Acceptance criteria	Results		
		<batch strength, use>	n	

i. Justification of proposed acceptance criteria for impurities:

**2.3.P.5.6 Justification of Specification(s)**

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

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

- (a) Source (including lot number) of primary reference standards or reference materials (e.g. Ph.Int., Ph.Eur., BP, USP, in-house) *not* discussed in 3.2.S.5:
- (b) Characterization and evaluation of non-official (e.g. not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g. elucidation of structure, certificate of analysis) *not* discussed in 3.2.S.5:
- (c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard) *not* discussed in 3.2.S.5:

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

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

Description (including materials construction)	Strength	Unit count or fill size	Container size

Summary of specifications of each primary and functional secondary (e.g. foil pouches) packaging components:



**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

<b>Packaging component</b>	<b>Specifications (list parameters e.g. identification (IR))</b>
HDPE bottle	
PP cap	
Induction sealed liners	
Blister films (PVC, etc)	
Aluminum foil backing	
etc.	

(a) Other information on the container closure system(s):

**2.3.P.8 Stability**

*2.3.P.8.1 Stability Summary and Conclusions*

(a) Summary of stress testing and results (e.g. photostability studies, cyclic studies, freeze-thaw studies):

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

<b>Storage condition (°C, % RH)</b>	<b>Strength and batch number</b>	<b>Batch size</b>	<b>Container closure system</b>	<b>Completed proposed) intervals</b>	<b>(an the</b>

Summary of the stability results observed for the above accelerated and long-term studies:

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

Test	Results
Description	
Moisture	
Impurities	
Assay	
etc.	

Test	Results

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

Container closure system	Storage statement	Shelf-life

**2.3.P.8.2 Post-approval Stability Protocol and Stability Commitment**

(a) Stability protocol for *Primary stability batches* (e.g. storage conditions (including tolerances), batch numbers and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details
Storage condition(s) (°C, % RH)	
Batch number(s) / batch size(s)	

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	

Parameter	Details
Testing frequency	
Container closure system(s)	

(a) Stability protocol for *Commitment batches* (e.g. storage conditions (including tolerances), batch numbers (if known) and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch number(s) / batch size(s)	<not less than three production batches in each container closure system>	
Tests and acceptance  Criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing Frequency		
Container Closure System(s)		

c) Stability protocol for Ongoing batches (e.g. storage conditions (including tolerances), number of batches per strength and batch sizes, tests and acceptance criteria, testing frequency, container closure system(s)):

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

Parameter	Details	
Storage condition(s) (°C, % RH)		
Batch size(s), annual allocation	<at least one production batch per year (unless none produced that year) in each container closure system >	
Tests and acceptance Criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

**2.3.P.8.3 Stability Data**

- (a) The actual stability results should be provided in *Module 3*.
- (b) Summary of analytical procedures and validation information for those procedures *not* previously summarized in 2.3.P.5 (e.g. analytical procedures used only for stability studies):
- (c) Bracketing and matrixing design and justification for *Commitment* and/or *Ongoing stability batches*, if applicable:

**2.3.A APPENDICES**

**2.3.A.1 Facilities and Equipment**

- (a) Summary of information on facilities and equipment, in addition to the information

## **ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

provided in other sections of the submission: Not applicable.

### **2.3.A.2 Adventitious Agents Safety Evaluation**

- (a) Summary of the information assessing the risk with respect to potential contamination with adventitious agents: Not applicable.

### **2.3.A.3 Excipients**

- (a) Summary of the details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical and/or clinical) for the novel excipients: Not applicable. Novel excipients are not accepted in the Prequalification Programme. See quality guideline for definition.
- (b)(b)

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

**2.3.R REGIONAL INFORMATION**

**2.3.R.1 Production Documentation**

**2.3.R.1.1 Executed Production Documents**

- (a) List of batches (including strengths) for which executed production documents have been provided (e.g. comparative bioavailability or biowaiver batches):

**2.3.R.1.2 Master Production Documents**

- (a) The blank master production documents for each strength, proposed commercial batch size and manufacturing facility should be provided in *Module 3*.

**2.3.R.2 Analytical Procedures and Validation Information**

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES	
ATTACHMENT NUMBER:	

HPLC Method Summary		Volume/Page:
Method name:		
Method code:		
Column(s) / temperature (if other than ambient):		
Mobile phase (specify gradient program, if applicable):		
Detector (and wavelength, if applicable):		
Flow rate:		
Injection volume:		

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

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 API or impurity reference standard(s)):	
Other information (specify):	
<b>ATTACHMENT NUMBER:</b>	

**ANNEX VI: QUALITY OVERALL SUMMARY(QOS)**

<b>Validation Summary</b>	<b>Volume/Page:</b>			
<b>Analytes:</b>				
Typical retention times (RT)				
Relative retention times (RT <sub>Imp.</sub> /RT <sub>API</sub> or Int. Std.):				
Relative response factor (RF <sub>Imp.</sub> /RF <sub>API</sub> ):				
<b>Specificity:</b>				
<b>Linearity / Range:</b> Number of concentrations: Range (expressed as % -All): Slope: Y-intercept: Correlation    coefficient (r <sup>2</sup> )				
<b>Accuracy:</b> Number of replicates: Percent    recovery (avg/RSD):				
<b>Precision / Repeatability:</b> (intra-assay precision) Result (avg/RSD): Conc.(s) (expressed as % -All): Number of replicates:				
<b>Precision / Intermediate Precision:</b> (days/analysts/equipment) Parameter(s) altered: Result (avg/RSD):				
<b>Limit of Detection (LOD):</b> (expressed as % -All)				
<b>Limit of Quantitation (LOQ):</b> (expressed as % -All)				
<b>Robustness:</b> Stability of solutions:  Other variables/effects:				
<b>Typical chromatograms or spectra may be found in:</b>				
<b>Company(s) responsible for method validation:</b>				
<b>Other information (specify):</b>				



## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

### **General Instructions:**

Please review all the instructions thoroughly and carefully prior to completing the Bioequivalence Trial Information Form (BTIF).

Provide as much detailed, accurate and final information as possible. Note that the greyed areas are NOT to be filled in by the applicant but are for THE AUTHORITY use ONLY!

Please state the exact location (Annex number) of appended documents in the relevant sections of the BTIF. For example, in **section 3.4.3.1** under **point b**), indicate in which Annex (number) the Certificate of Analysis can be found. This procedure must be followed throughout the entire document where location of annexed documents is requested.

Before submitting the completed BTIF, kindly check that you have provided all requested information and enclosed all requested documents.

Should you have any questions regarding this Form, please contact THE AUTHORITY.

A properly filled out and signed original copy of the BTIF with all its annexes (including a copy on CD-ROM) must be submitted to THE AUTHORITY together with the bioequivalence part of the dossier.

## ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION

ASSESSMENT REPORT FOR GENERIC VPP

NOT REGISTERED IN VICH REGIONS OR RELATED COUNTRIES

### BIOEQUIVALENCE PART OF A NEW DOSSIER

Reference of the session		
Date		
Type of product		
Type of dossier	<b>EFFICACY</b>	
Type of submission	<b>NEW</b>	
First assessor	Name	Signature
Second assessor	Name	Signature
Quality assessor (e.g., when dissolution profiles are submitted for comparison of the compositions of clinical, stability and validation batches, or a biowaiver for additional strengths is requested.)	Name	Signature
Reference Number		
Date of the submission		
Number of binders		
SPC , PIL submitted	(state location in submission)	
SPC, PIL, Package Labelling acceptable	Yes: _____ / No: _____	
Proprietary Product Name (if relevant)		
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.		
Conclusion of the assessment	<b>ACCEPTED (no outstanding issues)</b> <b>ADDITIONAL DATA REQUESTED</b> <b>REJECTED</b> <i>(please delete the wrong entries)</i>	
Name and complete address of the supplier (Applicant of the dossier)		
Name and address of the Contract Research Organization(s) where the clinical studies proving efficacy and safety of the product were conducted. <i>(Add as much rows as necessary)</i>		

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

This product assessment report should be written in clear unambiguous language referring to deficiencies or lack of data submitted, as communication with the manufacturer may result from the assessment.

### **BIOEQUIVALENCE TRIAL INFORMATION**

#### **1.0 SUMMARY**

##### **1.1 Summary of bioequivalence studies performed**

*(Provide a brief description of each comparative bioavailability study included in the submission)*

1.2 Tabulation of the composition of the formulation(s) proposed for marketing and those used for bioequivalence studies

(State the location of the master formulae in the quality part of the submission)

(Tabulate the composition of each product strength using the table below. For solid oral dosage forms the table should contain only the ingredients in tablet core /contents of a capsule. A copy of the table should be filled in for the film coating / hard capsule, if any.

**Important:** If the formulation proposed for marketing and those used for bioequivalence studies are not identical, copies of this table should be filled in for each formulation with clear identification in which bioequivalence study the respective formulation was used)

**ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

<b>Composition of the batches used for bioequivalence studies</b>					
Batch number					
Batch size (number of unit doses) <sup>1</sup>					
Comments, if any					
Comparison of unit dose compositions and of clinical VPP batches (duplicate this table for each strength, if compositions are different)					
Ingredients (and quality standard)	Function	Unit dose (mg)	Unit dose (%)	Biobatch (kg)	Biobatch (%)
<b>Total</b>					
Equivalence of the compositions or justified differences					
Maximum intended commercial batch size					

<sup>1</sup> Bioequivalence batches should be at least of pilot scale (10% of production scale or 100,000 capsules/tablets whichever is the greater) and manufacturing method should be the same as for production scale.

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

### **2.0 HAS COMPARATIVE BIOAVAILABILITY DATA BEEN SUBMITTED FOR ALL STRENGTHS?**

(If comparative bioavailability data has not been submitted for all strengths, provide a scientific justification for not submitting such data; append copies of all references cited in the justification. Justification should include – but is not limited to – argumentation related to dose- proportional composition, dose-linearity of pharmacokinetics (C<sub>max</sub> and AUC<sub>0-∞</sub>), discriminatory (with regard to bioavailability differences) power of dissolution tests employed).

Sections 3.0 – 11.0 below should be copied and completed separately for each bioequivalence study performed.

### **3.0 CLINICAL STUDY REPORT**

Study number:

Study Title:

Location of Study Protocol:

Start and stop dates for each phase of the clinical study: Dates of product administration

#### **3.1 ETHICS**

a) Name of review committee, date of approval of protocol and consent form, location of approval letter in the submission

b) State location of a reference copy of the informed consent form

#### **3.2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE**

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

- a) Name of principal investigator(s) (*State location of c.v. in the submission*)
- b) Clinical Facility (*Name and full mailing address*)
- c) Clinical Laboratories (*Name and full mailing address*)
- d) Analytical Laboratories (*Name and full mailing address*)
- e) Company performing pharmacokinetic/statistical analysis (*Name and full mailing address*)

### **3.3 STUDY OBJECTIVES**

Briefly state the study objectives.

### **3.4 INVESTIGATIONAL PLAN**

#### **3.4.1 Overall Study Design and Plan – Description**

(Describe the type of study design employed in 1-2 sentences)

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

### **3.4.2 Selection of Study Population**

#### **3.4.2.1 Inclusion Criteria**

#### **3.4.2.2 Exclusion Criteria**

(List the exclusion criteria applied to subjects)

#### **3.4.2.3 Removal of Trial subjects from Trial or Assessment**

##### **(a) Number of subjects enrolled in the study**

(All subjects including alternates, withdrawals, and dropout)

##### **(b) Withdrawals**

(Identify each withdrawal by subject and provide the reason for withdrawal and at what point in the study the withdrawal occurred)

#### **3.4.2.4 Health Verification**

*(State location of the individual data included in the submission)*

##### **a) List criteria used and all tests performed in order to judge health status**

##### **b) Indicate when tests were performed**

##### **c) Study site normal values**

*(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)*

##### **d) Report any results that were outside of study site normal values**

*(State location in submission of the summary of anomalous values)*

#### **3.4.2.5. Removal of Trial subjects from Trial or Assessment**

##### **(a) Number of subjects enrolled in the study**

(All subjects including alternates, withdrawals, and dropouts)

##### **(b) Alternates**

(Please note: Generally, all subjects enrolled in the study should be included in the data set i.e., alternate subjects are strongly discouraged. However, in cases where there are alternate subjects,

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

describe the procedure of including/excluding the alternates and whether alternates have been included in the study)

### (c) Withdrawals/dropouts

(Identify each withdrawal/dropout by subject and provide the reason for withdrawal/dropout and at what point in the study the withdrawal/dropout occurred)

### 3.4.3 Products Administered

#### 3.4.3.1 Test Product

- (a) Batch number, size and date of manufacture for the test product
- (b) Potency (measured content) of test product as a percentage of label claim as per validated assay method

(This information should be cross-referenced to the location of the certificate of analysis in the submission)

#### 3.4.3.2 Comparator (Reference) Product

(Append to this template a copy of product labelling (snap shot of the box, on which the name of the product, name and address of the manufacturer, batch number, and expiry date are clearly visible on the labelling).

- (a) Name and manufacturer of the Comparator product
- (b) Batch number and expiry date for the Comparator product
- (c) Purchase, shipment, storage of the Comparator product

(This information should be cross-referenced to location in submission of documents (e.g. receipts) proving conditions)



## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

- (d) Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory and under the same conditions as the test product

(This information should be cross-referenced to the location of the certificate of analysis in the submission)

- (e) Justification of choice of reference product

(Provide short summary here and cross-reference to location of comprehensive justification in study protocol)

### 3.4.4 Selection of Doses in the Study

#### (a) State dose administered

(Indicate the number of dosage units comprising a single dose, e.g., 400 mg as 1 x 400 mg or 2 x 200 mg tablets)

### 3.4.5 Selection and Timing of Dose for Each Subject

- (a) State volume and type of fluid consumed with dose,
- (b) Interval between doses (i.e., length of washout),
- (c) Protocol for the administration of food and fluid,
- (d) Restrictions on posture and physical activity during the study

### 3.4.6 Blinding

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

1.4.6.1 Identify which of the following were blinded. If any of the groups were not blinded, provide a justification for not doing so

- a) study monitors: Yes  / No  If No, justify:
- b) subjects: Yes  / No  If No, justify:
- c) analysts: Yes  / No  If No, justify: \_\_\_\_\_

3.4.6.2 Identify who held the study code and when the code was broken

### 3.4.7 Drug Concentration Measurements

#### 3.4.7.1 Biological fluid(s) sampled

#### 3.4.7.2 Sampling Protocol

- (a) Number of samples collected per subject
- (b) Volume of fluid collected per sample
- (c) Total volume of fluid collected per subject per phase of the study
- (d) List the study sampling times
- (e) Identify any deviations from the sampling protocol (State location of summary in the submission)

(Describe and explain reasons for deviations from sampling protocol. Comment on impact on study.

Indicate whether the deviations were accounted for in the pharmacokinetic analysis)

#### 3.4.7.3 Sample Handling

- (a) Describe the method of sample collection
- (b) Describe sample handling and storage procedures

## **3.5 COMMENTS FROM REVIEW OF SECTION 3.0 – THE AUTHORITY USE ONLY**

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

### **4.0 TRIAL SUBJECTS**

#### **4.1 Demographic and Other Baseline Characteristics**

- (a) Identify study population
- (b) Summary of ethnic origin and gender of subjects
- (c) Identify subjects noted to have special characteristics and state notable characteristics
- (d) (e.g., fast acetylators of debrisoquine)
- (e) Range and mean age  $\pm$  SD of subjects
- (f) Range and weight  $\pm$  SD of subjects
- (g) Identify subjects whose ratio is not within 15% of the values given on a standard height/weight table

#### **4.2 Subjects who smoke**

- (a) Number of smokers included in the study;
- (b) Indicate how many cigarettes smoked per day per subject;
- (c) Comment on the impact of study.

#### **4.3 COMMENTS FROM REVIEW OF SECTION 4.0 – THE AUTHORITY USE ONLY**

### **5.0 PROTOCOL DEVIATIONS**

#### **5.1 Protocol deviations during the clinical study**

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

(Describe any such deviations and discuss their implications with respect to bioequivalence)

### **5.2 COMMENTS FROM REVIEW OF SECTION 5.0 – THE AUTHORITY USE ONLY**

## **6.0 SAFETY EVALUATION**

### **6.1 Identify adverse events observed**

(List any adverse events by subject number. State whether a reaction occurred following administration of the test or reference product, identify any causal relationships, and note any treatments required. State location of this summary in the submission)

(Discuss the implications of the observed adverse events with respect to bioequivalence)

### **6.2 COMMENTS FROM REVIEW OF SECTION 6.0 – THE AUTHORITY USE ONLY**

## **7.0 EFFICACY EVALUATION –**

Efficacy Results and Tabulations of Individual Trial Subjects Data

### **7.1 Presentation of Data**

- (a) State location in submission of tables of mean and individual subject concentrations
- (b) State location in submission of (mean and individual) linear and semi-logarithmic subject drug concentration vs. time plots

## ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION

### 7.2. Pharmacokinetic (PK) Parameters

- (a) State how the pharmacokinetic parameters were calculated/obtained for  $AUC_{0-inf}$ ,  $AUC_{0-t}$ ,  $C_{max}$ ,  $t_{max}$ , the elimination rate constant, and  $t_{1/2}$  (indicate location of description in protocol)
- (b) State whether actual sampling time points were used for estimation of the pharmacokinetic parameters
- (c) Complete the table below

Parameter	Test			Reference		
	Arithmetic mean	Standard deviation	Inter individual coefficient of variation (%)	Arithmetic mean	Standard deviation	Inter individual coefficient of variation (%)
$AUC_T$ (Unit)						
$AUC_I$ (units)						
$C_{max}$ (units)						
$T_{max}$ (units)						
$T_{1/2}$ (units)						

**ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

- (a) (State method of AUC calculation and method of extrapolation. Indicate location of description in protocol)
- (b) Ratio of AUCT to AUCI

(State mean ratio for both test and reference, state location in submission where individual ratios can be found,)

7.3 Statistical Analysis

(Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUCT and CMAX and other relevant parameters, e.g. in the case of steady-state designs, AUC $\tau$ , CMAX, and CMIN; state software which has been used for computing ANOVA)

- (a) Geometric means, Results from ANOVA, Degrees of Freedom (DF) and derived CV (intraindividual)

Parameter Test	Reference	Ratio of Geometric Means	90% Confidence Interval	DF	CV(%)
AUC <sub>T</sub> (Unit)					
AUC <sub>I</sub> (units)					
C <sub>max</sub> (units)					

- (b) Period and/or sequence effects

(State whether any period- and/or sequence-effects have been found. If yes, provide short discussion of effects here, and state location in submission where comprehensive explanation is provided)

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

### **(c) Comparison of the results**

(Compare the results, including mean values, inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), WHOPARs), and copies of the references used should be appended to this document)

### **7.4 DISCUSSION OF RESULTS**

(State location of the discussion of the results in the submission. If the discussion currently included in the study report does not include comparisons of results, including inter- and intraindividual variability, of this study with published results (literature, product information of reference product (innovator), such a discussion should be provided here and copies of the references used should be appended to this document)

### **7.5 COMMENTS FROM REVIEW OF SECTION 7.0 – THE AUTHORITY USE ONLY**

#### **8.1 Analytical Technique**

##### 8.1.1 Analytical protocol

(State the location of the analytical protocol)

##### 8.1.2 Identify analyte(s) monitored

##### 8.1.3 Comment about source and validity of reference standard

##### 8.1.4 Identify analytical technique employed

##### 8.1.5 Identify method of detection

##### 8.1.6 Identify internal standard

##### 8.1.7 If based on a published procedure, state reference citation

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

8.1.8 Identify any deviations from protocol

8.1.9 Dates of subject sample analysis

8.1.10 Longest period of subject sample storage

(Identify the time elapsed between the first day of sample collection and the last day of subject sample analysis)

8.1.11 State whether all samples for a given subject were analysed together in a single analysis run

8.2 Standard Curves

(State location in submission of tabulated raw data and back calculated data with descriptive statistics)

(a) List number and concentration of calibration standards used

(b) State number of curves run during the study

(c) Summarize descriptive data including slope, intercept, correlation coefficients

(d) Describe the regression model used including any weighting

(e) State the limit of quantitation (LOQ)

(Summarize inter-day and intra-day precision and accuracy at the LOQ)



## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

### 8.3 Quality Control Samples

- (a) Identify the concentrations of the QC samples, their date of preparation and the storage conditions employed prior to their analysis
- (b) State the number of QC samples in each analytical run per concentration

### 8.4 Precision and Accuracy

- (a) Summarize inter-day and intra-day precision and accuracy of QC samples analysed during subject sample analysis and inter-day precision of back-calculated standards

### 8.5 Repeat Analysis

- (a) List repeats by sample identification and include the following information for each repeat: initial value; reason for repeat; repeat value(s); accepted value; and reason for acceptance;
- (b) Report the number of repeats as a percentage of the total number samples assayed

### 8.6 Chromatograms

(State the location in the submission where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five. A complete set includes standards, QC samples, pre-dose and post-dose subject samples for both phases. Each chromatogram should be clearly labelled with respect to the following: date of analysis; subject ID number; study period; sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; peak heights and/or areas)

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

### **8.7 COMMENTS FROM REVIEW OF SECTION 8.0 – THE AUTHORITY USE ONLY**

### **9.0 ANALYTICAL VALIDATION REPORT**

#### 9.1 Precision and Accuracy

(a) Summarize inter-day and intra-day accuracy and precision during assay validation

(b) Summarize inter-day and intra-day accuracy and precision during assay re validation (If applicable)

#### 9.2 Stability

(For each section provide the location of the raw data, a description of the methodology employed and a summary of the data)

(a) Summarize data on long-term storage stability

(b) Summarize data on freeze-thaw stability

(c) Summarize data on bench top stability

(d) Summarize data on autosampler storage stability

(e) Summarize data from any other stability studies conducted

(e.g., stock solution stability)

#### 9.3 Specificity

(Methods to verify specificity against endogenous/exogenous compounds & results)

#### 9.4 Matrix effect (in case of MS detection)

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

(Methods to verify the matrix effect & results)

### 9.5 Recovery

(Method and results of assessment for analyte and internal standard including mean and CV%)

### 9.6 COMMENTS FROM REVIEW OF SECTION 9.0 – THE AUTHORITY USE ONLY

## **10.0 QUALITY ASSURANCE**

### 10.1 Internal quality assurance methods

(State locations in the submission where internal quality assurance methods and results are described for each of study sites (see 3.2 b-d)

10.2 <u>Monitoring, Auditing, Inspections</u>
---

(Provide a list of all monitoring and auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in the submission of the respective reports for each of study sites (see 3.2 b-d)

### 10.3 COMMENTS FROM REVIEW OF SECTION 10 – THE AUTHORITY USE ONLY

**CONCLUSIONS AND RECOMMENDATIONS – THE AUTHORITY USE ONLY**

**POINTS TO BE COMMUNICATED TO THE MANUFACTURER**

## **ANNEX VII: PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION**

### **(b) General remark, if applicable**

Each application should be considered as a stand-alone submission. Observations of evaluators already clarified through correspondence with THE AUTHORITY should be adopted in the new application as amended in order to avoid wasting evaluators' time.

### **(c) Overall conclusion**

Please fill in the relevant conclusion, based on the review of the data on efficacy and safety, in the first part of the document.

*Please copy all relevant information to be communicated to the manufacturer in the corresponding letter and save it accordingly.*

## **RECOMMENDATIONS FOR INSPECTION**

## ANNEX VIII: BIOWAIVER APPLICATION FORM

### Biopharmaceutics Classification System (BCS)

This application form is designed to facilitate information exchange between the Applicant and THE AUTHORITY, if the Applicant seeks to waive bioequivalence studies, based on the Biopharmaceutics Classification System (BCS). This form is not to be used, if a biowaiver is applied for additional strength(s) of the submitted product(s), in which situation a separate

–*Biowaiver Application Form: Additional Strengths* should be used.

*Kenya FDA has identified the Active Pharmaceutical Ingredients (APIs) that are eligible for a BCS-based biowaiver application. Therefore, in some cases it is not necessary to provide data to support the BCS classification of the respective API(s) in the application i.e. data supporting the drug substance solubility or permeability class.*

#### **General Instructions:**

- Please review all the instructions thoroughly and carefully prior to completing the current Application Form.
- Provide as much detailed, accurate and final information as possible
- Please enter the data and information directly following the greyed areas.
- Please enclose the required documentation in full and state in the relevant sections of the Application Form the exact location (Annex number) of the appended documents.
- Please provide the document as an MS Word file
- Do not paste snap-shots in the document

## ANNEX VIII: BIOWAIVER APPLICATION FORM

- Please enclose the required documentation in full and state in the relevant sections of the Application Form the exact location (Annex number) of the appended document.
- The appended electronic document should be clearly identified in their file names, which should include the product name and Annex number.
- Before submitting the completed Application Form, kindly check that you have provided all requested information and enclosed all requested documents.
- Should you have any questions regarding this procedure, please contact THE AUTHORITY.

The signed paper version of this Biowaiver Application Form together with Annexes (and their electronic copies on CD-ROM) should be included to the bioequivalence part of the submitted dossier and sent by surface mail to THE AUTHORITY.

### 1.0 Administrative data

#### 1.1 Trade name of the test product

1.2	<i>INN of active ingredient(s)</i>
<i>&lt; Please enter information here &gt;</i>	
1.3	<i>Dosage form and strength</i>

**ANNEX VIII: BIOWAIVER APPLICATION FORM**

*< Please enter information here >*

**1.1**      ***Product EAC Reference number (if product dossier has been accepted for EAC assessment)***

*< Please enter information here >*

**1.5**      **Name of applicant and official addresses**

*< Please enter information here >*

**1.2**      **Name of manufacturer of finished product and full physical address of the manufacturing site**

*< Please enter information here >*

**1.3**      ***Name and address of the laboratory or Contract Research Organisation(s) where the BCS-based biowaiver dissolution studies were conducted.***

*< Please enter information here >*

**ANNEX VIII: BIOWAIVER APPLICATION FORM**

**2.0 Test product**

***2.1 Tabulation of the composition of the formulation(s) proposed for marketing and those used for comparative dissolution studies***

- Please state the location of the master formulae in the specific part of the dossier of the submission.
- Tabulate the composition of each product strength using the table 2.1.1
- For solid oral dosage forms the table should contain only the ingredients in tablet core or contents of capsule. A copy of the table should be filled in for the film coating/hard gelatine capsule, if any.
- Biowaiver batches should be at least of pilot scale (10% of production scale or 100,000 capsules or tablets whichever is greater) and manufacturing method should be the same as for production scale.

**Please note:** If the formulation proposed for marketing and those used for comparative dissolution studies are not identical, copies of this table should be filled in for each formulation for clear identification in which study the respective formulation was used.

***2.1.1 Composition of the batches used for comparative dissolution studies***

Batch number	
Batch size (number of unit doses)	



**ANNEX VIII: BIOWAIVER APPLICATION FORM**

Date of manufacture				
Comments, if any				
Comparison of unit dose compositions (duplicate this table for each strength, if compositions are different)				
Ingredients (Quality standard)	Unit dose (mg)	Unit dose (%)		
Equivalence of the compositions or justified differences				
<p><b>2.2 Potency (<i>measured content</i>) of test product as a percentage of label claim as per validated assay method</b></p> <p>This information should be cross-referenced to the location of certificate of analysis (CoA) in this biowaiver submission.</p>				
<p>&lt; Please enter information here &gt;</p>				

## ANNEX VIII: BIOWAIVER APPLICATION FORM

***COMMENTS FROM REVIEW OF SECTION 2.0 - THE AUTHORITY USE ONLY***

### 2.0 Comparator product

#### **3.1 Comparator product**

Please enclose a copy of product labelling (summary of product characteristics), as authorized in country of purchase, and translation into English, if appropriate.

#### **3.2 Name and manufacturer of the comparator product (Include full physical address of the manufacturing site)**

< Please enter information here >

#### **3.3 Qualitative (and quantitative, if available) information on the composition of the comparator product**

Please tabulate the composition of the comparator product based on available information and state the source of this information.

##### **3.3.1 Composition of the comparator product used in dissolution studies**

Batch number	
Expiry date	

**ANNEX VIII: BIOWAIVER APPLICATION FORM**

Comments, if any		
Ingredients and reference standards used	Unit dose (mg)	Unit dose (%)
<p><b>3.4 Purchase, shipment and storage of the comparator product</b> Please attach relevant copies of documents (e.g. receipts) proving the stated conditions.</p>		
<p>&lt; Please enter information here &gt;</p>		
<p><b>3.5 Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory under the same conditions as the test product.</b></p> <p>This information should be cross-referenced to the location of certificate of analysis (CoA) in this biowaiver submission.</p>		
<p>&lt; Please enter information here &gt;</p>		
<p><b>COMMENTS FROM REVIEW OF SECTION 3.0 - THE AUTHORITY USE ONLY</b></p>		

**ANNEX VIII: BIOWAIVER APPLICATION FORM**

**3.0 Comparison of test and comparator products**

**3.1 Formulation**

**4.1.1 Identify any excipients present in either product that are known to impact on in vivo absorption processes**

A literature-based summary of the mechanism by which these effects are known to occur should be included and relevant full discussion enclosed, if applicable.

*< Please enter information here >*

**4.2 Identify all qualitative (and quantitative, if available) differences between the compositions of the test and comparator products**

The data obtained and methods used for the determination of the quantitative composition of the comparator product as required by the guidance documents should be summarized here for assessment

*< Please enter information here >*

**4.3 Provide a detailed comment on the impact of any differences between the compositions of the test and comparator products with respect to drug release and in vivo absorption**

*< Please enter information here >*

**COMMENTS FROM REVIEW OF SECTION 4.0 - THE AUTHORITY USE ONLY**

**4.0 Comparative in vitro dissolution**

Information regarding the comparative dissolution studies should be included below to provide adequate evidence supporting the biowaiver request. Comparative

**ANNEX VIII: BIOWAIVER APPLICATION FORM**

dissolution data will be reviewed during the assessment of the Quality part of the dossier

Please state the location of:

- the dissolution study protocol(s) in this biowaiver application
- the dissolution study report(s) in this biowaiver application
- the analytical method validation report in this biowaiver application

< *Please enter information here* >

**5.1 Summary of the dissolution conditions and method described in the study report(s)**

Summary provided below should include the composition, temperature, volume, and method of de-aeration of the dissolution media, the type of apparatus employed, the agitation speed(s) employed, the number of units employed, the method of sample collection including sampling times, sample handling, and sample storage. Deviations from the sampling protocol should also be reported

**5.1.1 Dissolution media: Composition, temperature, volume, and method of de-aeration**

< *Please enter information here* >

**5.1.2 Type of apparatus and agitation speed(s) employed**

< *Please enter information here* >

**ANNEX VIII: BIOWAIVER APPLICATION FORM**

**5.1.3 Number of units employed**

*< Please enter information here >*

**5.1.4 Sample collection: method of collection, sampling times, sample handling and storage**

*< Please enter information here >*

**5.1.5 Deviations from sampling protocol**

*< Please enter information here >*

**5.1.6 Dissolution media: Composition, temperature, volume, and method of de-aeration**

*< Please enter information here >*

**5.2 Summarize the results of the dissolution study(s)**

Please provide a tabulated summary of individual and mean results with % CV, graphic summary, and any calculations used to determine the similarity of profiles for each set of experimental conditions.

## ANNEX VIII: BIOWAIVER APPLICATION FORM

< Please enter information here >

### **5.3 Provide discussions and conclusions taken from dissolution study(s)**

Please provide a summary statement of the studies performed.

< Please enter information here >

**COMMENTS FROM REVIEW OF SECTION 5.0 - THE AUTHORITY USE ONLY**

## 6.0 Quality assurance

### **6.1 Internal quality assurance methods**

Please state location in this biowaiver application where internal quality assurance methods and results are described for each of the study sites

< Please enter information here >

### **6.2 Monitoring, Auditing, Inspections**

Provide a list of all auditing reports of the study, and of recent inspections of study sites by regulatory agencies. State locations in this biowaiver application of the respective reports for each of the study sites e.g., analytical laboratory, laboratory where dissolution studies were performed

*< Please enter information here >*

**COMMENTS FROM REVIEW OF SECTION 6.0 – THE AUTHORITY USE ONLY**

**Declaration**

I, the undersigned, certify that the information provided in this application and the attached document is correct and true

Signed on behalf of <company> Date

Name and title

*< Please enter information here >*

**CONCLUSIONS AND RECOMMENDATIONS – THE AUTHORITY USE ONLY**