GUIDELINE FOR MARKETING AUTHORISATIONS OF

VETERINARY PHARMACEUTICAL PRODUCTS IN EAC COMMUNITY

Draft agreed by Technical Working Group	15th Nov 2018
Draft released for consultation by representatives of East African region regulatory agencies	3rd Dec 2018
End of consultation period	31st Dec 2018
EAC code	PSS/1/1/21/92
Enters into force	08 February 2019
Review version 2	24th June 2022

JULY 2022

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ABBREVIATIONS

API	-	Active Pharmaceutical Ingredient
ATC	-	Anatomic Therapeutic Chemical Classification
AUC	-	Area Under the Plasma Concentration Time Curve
BAN	-	British Approved Name
BP	-	British Pharmacopoeia
BSE	-	Bovine Spongiform Encephalopathy
CAS	-	Chemical Abstract Service
CEP	-	European Certificate of Suitability
Cmax	-	Maximum plasma concentration
CMC		Chemistry Manufacturing and Control
CoA	-	Certificate of Analysis
CPP	-	Certificate of Pharmaceutical Product
CTD		Common Technical Document
DMF	-	Drug Master File
EAC	-	East African Community
EU	-	European Union
FDC	-	Fixed Dose Combination
FPP	-	Finished Pharmaceutical Products
GMP	-	Good Manufacturing Practice
ICH	-	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INN	-	International Non-proprietary Name JAN
	-	Japanese Accepted Name
JP	-	Japanese Pharmacopoeia
LOD	-	Loss on Drying
MedDRA	-	Medical Dictionary for Drug Regulatory Authorities
MDD	-	Maximum Daily Dose
M.R	-	Modified Release
Mg	-	Milligram
Ml	-	Millilitre
MRA	-	Medicines Regulatory Authority
MRL	-	Maximum Residue Limits
NCE	-	New Chemical Entity
NMT	-	Not More Than
PhEur	-	European Pharmacopoeia
PD		Pharmaco-dynamics
PD		Product Dossier
QA	-	Quality Assurance

QIS	-	Quality Information Summary
QOS	-	Quality Overall Summary
QTPP	-	Quality Target Product Profile
RH	-	Relative Humidity
SMACS	-	Starting Materials Certification Scheme
SMF	-	Site Master File
SST	-	System Suitability Tests
TFDCA	-	Tanzania Food, Drugs and Cosmetics Act
TSE	-	Transmissible Spongiform Encephalopathy
USP		United States Pharmacopoeia
VICH	-	International Conference on Harmonization of Technical Requirements for Registration of Veterinary Pharmaceutical Products
VPP	-	Veterinary Pharmaceutical Product

FOREWORD

The East African Community (EAC) is a regional intergovernmental organization of six Partner States consisting of the Republics of Burundi, Kenya, Rwanda, South Sudan, the United Republic of Tanzania and Uganda. Veterinary pharmaceutical products in this region are regulated under different Ministries/Authorities namely Tanzania Food and Drugs Authority (TFDA; the National Drug Authority (NDA) of Uganda; Ministry of Environment, Agriculture and Livestock of the Republic of Burundi; Veterinary Medicines Directorate of Kenya; Rwanda Agricultural Board and the Ministry of Livestock and Fisheries of the Republic of South Sudan.

With the support of the Livestock desk at the EAC Secretariat, EAC Partner States have developed harmonised tools for registration of Veterinary Immunological Products (IVPs) and commenced harmonised registrations of IVPs in the EAC. EAC is now ready to expand this scope of harmonisation of veterinary products to cover harmonised registration of Veterinary Pharmaceutical Products.

The initiative aims at increasing the availability of affordable, safe and quality veterinary medicinal products to the EAC region within a short period of time compared to national applications where the processes are varied and time consuming. Before this initiative, applicants must apply separately to each Partner State where they wish to market the products by submitting application as per requirements of each National Regulatory Authority (NRA). All the hurdles associated with national registrations is solved under MRP in that it allows Marketing Authorisations to be issued without long delays, accelerates availability of good quality, safe and efficacious veterinary pharmaceuticals, avoids duplication of assessment, improves predictability, builds trust between Regulators and allows for rapid introduction of new veterinary pharmaceuticals.

Once MRP starts, National Marketing Authorisations will continue to be applied for and issued, in parallel with MRPs. For applicants wishing to have a Marketing Authorisation (MA) for a product in more than one Partner State, they are encouraged to use the Mutual Recognition Procedure (MRP).

This guideline, together with other technical documents such as an Application Form and SPC and labelling templates developed by the TWG, are controlled documents which are coded and entered into the EAC's document website, where they are maintained and revised as necessary. The

guideline serves to guide applicants seeking Marketing Authorisations of veterinary pharmaceutical products in EAC region under MRP.

There will be periodic reviews of these guidelines through a process of consultation between country representatives and the veterinary medicines producers before new Guidelines are implemented.

A process for approval of specified emergency veterinary medicines should remain outside of MRP and be dealt with at a National level.

ACKNOWLEDGEMENTS

EAC appreciates the technical and financial support received from GALVmed in the development of this guideline.
The community would also like to thank in particular, the EAC Technical Working Group Members named; Dr. Gerard Nishemezwe (BDI) and Desire Ntakirutimana (BDI), Richard Gahungu (BDI), Prof. James Mbaria (KE), Dr. Nathan Songok (KE), Dr. Naphtali Mwanziki (KE), Dr. Adelaide Ayoyi (KE), Jean Claude Rukundo (RW), Isidore Gafarasi (RW) Christopher Migoha (URT), Dr. Emmanuel Mutakyahwa (URT), Dr. Solomon David Adwok (SSD), Dr. Jada Wani (SSD), Dr. Josephine Nanyanzi (UG), Dr. Noel Aineplan (UG). Daniel Etuko (UG) and extends appreciation to the NMRA for allowing their staff and experts to participate in this initiative. EAC further extends it appreciation to its Secretarial staff: Dr. Elizabeth Okello (EAC/GALVmed), Dr. David Balikowa (EAC) and Fahari Marwa (EAC), the Ex EAC colleagues, as well as the Director of PANVAC Nick Nwankpa and Gilly Cowan (a UK Consultant) who has been instrumental in the development of this document.

GALVmed is funded by the Bill & Melinda Gates Foundation and the UK Government. The views expressed in this document are those of the author and do not necessarily represent the views of the Bill & Melinda Gates Foundation nor the UK Government.

INTRODUCTION

The "Guidelines sets out procedures and requirements for the implementation of veterinary Pharmaceutical Products (VPPs) Registration through Common Technical Document (CTD). The guidelines are arranged as per the CTD format as follows:

Module 1: Administrative Requirements;

Module 2: The Quality Overall Summaries (QOS),

Module 3: The Quality Requirements for the Active Pharmaceutical Ingredients (API) and Finished Pharmaceutical Products (FPP),

Module 4: Pre-Clinical Data Requirements,

Module 5: Clinical Data Requirements

.

Adoption of the MRP is in line with Chapter 18, Article 108 (e) of the East African Community Treaty which provides for adoption of a common mechanism for ensuring the safety, quality and efficacy of products.

The principle of the proposed Mutual Recognition Procedure (MRP) is the acceptance of an authorisation for a medicinal product issued by one of the countries in a group of countries, such as the EAC Partner States, by the other countries in that group.

The general objective of the guidelines is to improve access to essential veterinary pharmaceutical products for prevention and treatment of priority disease conditions in the EAC region

These guidelines apply only to veterinary pharmaceutical products. In case of other products like IVPs, separate guidelines are available and these can be accessed online from the EAC Website;

http://www.eac.int/documents/category/livestock

GLOSSARY OF TERMS

For the purposes of these guidelines, the following phrases are defined as follows:

Active Pharmaceutical Ingredient
Means a substance or compound that is intended to be used in the manufacture of a veterinary pharmaceutical product as a therapeutically active compound (ingredient).

Applicant/Registrant or Marketing Authorization Holder (MAH)

Means a person who owns a formula or trademark of a veterinary pharmaceutical product, who may be a manufacturer or a person to whose order and specifications the product is manufactured and who shall be the registration holder and have the primary responsibility of the product in the EAC region.

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, vial, jar, box, packet, sachet or other receptacle which contains or is to contain in it, not being a capsule or other article in which the veterinary product is or is to be administered or consumed, and where any such receptacle is or is to be contained in another receptacle, 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 ~~e~~ such as a carton.

Veterinary pharmaceutical product

Means any substance or mixture of substances manufactured sold or represented for use in:

(a) The diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical or mental state, or the symptoms thereof, in animals;

(b) Restoring, correcting or beneficial modification of organic or mental functions in animals;

(c) Disinfection in premises in which veterinary medicines are manufactured, prepared or kept, ambulatory services, veterinary clinics, veterinary facilities and equipment;

(d) Articles intended for use as a component of any article specified in clause (a), (b) or (c); but does not include veterinary medical devices or their components, parts or accessories.

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 pharmacopoeias or those well documented in the literature and generally recognized as safe and effective for use as a veterinary medicine.

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 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.

Non-Prescription/General sale medicine

Means any medicine whose use does not need the direction or prescription by a veterinarian recognised under the Veterinary Act as it is prescribed in the national veterinary Acts in respective EAC Partner States.

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) based on documentation of efficacy, safety and quality (according to the requirements at the time of authorization).

Interchangeability

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

In-process control

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 also be regarded as part of in-process control.

Label

Means any tag, brand, mark, pictorial or other descriptive matter, written, printed, painted, 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, packaging, release, storage of finished veterinary pharmaceutical products and the related controls.

Manufacturer

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

Marketing authorization (registration)

Means an official authorization or registration of a veterinary pharmaceutical product by EAC Partner states involved in the Mutual Recognition Procedure for the purpose of marketing or free distribution after evaluation for quality, safety and efficacy.

New active veterinary pharmaceutical ingredient

Means a veterinary pharmaceutical product (active ingredient), including its salts, esters, derivatives, etc., which is not a subject of current pharmacopoeias.

New combination

Means a product containing medicines in combination (qualitative content and/or proportions) different from those veterinary products that are 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 product.

Pharmacopoeia

Means a current edition of the British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia, Japanese Pharmacopoeia and OIE Manual.

Retention fee
Means a fee paid annually to maintain marketing authorization in a partner state where it has been issued.

Specifications – expiry check or shelf life

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

Specifications - release

Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a veterinary 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 veterinary pharmaceutical product, but excluding packaging materials.

Validation
The documented act of proving that any procedure, process, equipment, materials, activity or system actually leads to the expected results.

Variation

Means a change to any aspect of a registered/marketing authorised 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.

Well-established medicines

Means APIs (not products) which:

- Have been marketed for at least five years in countries that undertake active post-marketing surveillance.
- Have been widely used in a sufficiently large number of animals to permit the assumption that safety and efficacy are well known; and
- Have the same route of administration and strength, and the same or similar indications as in those countries.

Well-established pharmaceutical products

Means pharmaceutical products which contain well established medicines and which:

- Have been marketed for at least five years in countries that undertake active post-marketing monitoring.
- Have been widely used in a sufficiently large number of animals to permit the assumption that safety and efficacy are well known; and have the same route of administration and strength, and the same or similar indications as in those countries.

WHO-type certificate

Means a certificate of veterinary pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

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. Generally, all the documents in Module 1, other than the annexes, can be provided in a single volume.

Products shall be evaluated on a First in First out (FIFO) basis and the timeline for review and communication to applicant shall be as prescribed in the Best Practice Guide for Mutual Recognition Procedures for the Registration of Veterinary Medicinal Product(s) in the EAC**. Link:** http://www.eac.int/documents/category/livestock REF: GL5-Best Practice Guide for MRP | CODE: PSS/1/1/21/81

1.1 Comprehensive Table of Contents for all Modules

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

1.2 Application letter

An application letter of not more than 500 words should be submitted with the product dossier indicating why the product should be registered. The letter should be signed by Marketing Authorization Holder.

1.3 Manufacturing and Marketing Authorization

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

1.4 Application Information

Application for the registration of a veterinary pharmaceutical product shall be made only by;

- The patent holder
- The manufacturer
- The Distributor authorised by the manufacturer or patent holder

The name, physical address, telephone number, fax number and e-mail address of the applicant shall be provided.

1.4.1 Language

All applications and supporting documents shall be as per T3 for SPC.

1.4.2 Application form

An application to register a veterinary pharmaceutical product for veterinary use must be accompanied by a completed Application Form (**Annex I**)

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

1.4.3 Data Presentation

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

Table I: Parts required for each type of pharmaceutical product

	Product type	**Parts required**				
		I	**II**	**III**	**IV**	**V**
		SPC	**API**	**FPP**	**Pre-clinical Pharmaco-toxicolgical**	**Clinical Safety and efficacy**
1	Innovator	√	√	√	√	√
2	Innovator fixed dose combination.	√	√	√	√	√
3	Innovator variants: either as single or composite variation in dosage level, form, route of administration, or indication.	√	√	√	Bridging studies data	Bridging studies data
4	Single active ingredient or Fixed dose combination generic.	√	√	√	x	x

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

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

1.5 Product Information and Labelling

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

1.5.1 Prescribing information (Summary of Product Characteristics)

All veterinary pharmaceuticals should be accompanied by SPC. The Prescribing information is not a promotional document. Statements of a promotional nature such as “x is the safest drug” are not acceptable.

An applicant shall prepare and present prescribing information in the contents and format as provided in;
T3 Template for SPC and Labelling of Veterinary Pharmaceutical Products https://www.eac.int/documents/category/livestock

1.5.2 Container labelling
Product should be labelled as prescribed in;
T3 Template for SPC and Labelling of Veterinary Pharmaceutical Productshttps://www.eac.int/documents/category/livestock

1.5.3 Information Leaflet

Every container of a veterinary pharmaceutical product shall be accompanied with information leaflet

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

The contents and format of the leaflet are as provided in;
T3 Template for SPC and Labelling of Veterinary Pharmaceutical Products https://www.eac.int/documents/category/livestock

1.5.4 Good Manufacturing Practice (GMP)

For all medicines, irrespective of the country of origin, all key manufacturing and/or processing steps in the production of active pharmaceutical ingredients and finished veterinary pharmaceutical products must be performed in plants that comply with EAC GMP guidelines. Attach/provide a WHO type certificate of GMP in the dossier. For more information on GMP requirements and application for GMP inspection, refer Compendium of Good Manufacturing Practices (GMP) Technical Documents for veterinary Mutual Recognition Procedure for veterinary Medicines Regulation in the East African Community available at EAC livestock websites: https://www.eac.int/documents/category/livestock

1.5.5 Product samples

Sufficient number of samples should be submitted together with the application preferably three (3) samples of each pack size from one batch proposed for commercial purpose should be submitted, otherwise additional samples shall request when need arise.

MODULE 2: OVERVIEW & SUMMARIES

2.1 Table of contents of Module 2

A table of content of module 2 should be provided.

2.2 CTD Introduction

A general introduction to the drug, including its pharmacological class, mode of actions and proposed clinical use.

2.3 Quality Overall Summary (QOS)

This is the CMC summary, intended to give the quality reviewer sufficient information from each section to provide an overview of Module 3. The Quality Overall Summary (QOS) is a summary that follows the scope and the outline of the Body of Data in Module 3. The QOS should not include information, data or justification that was not already included in Module 3 or in other parts of the CTD.

The QOS template is in **annex III** of this guideline. The QOS should be provided in both word and PDF version. The word version is a must.

Complete the Quality Overall Summary (QOS) following the following guidance below:

2.3.S Drug Substances (API)

2.3. S.1 General Information)

Information from 3.2.S.1 should be included.

2.3. S.2 Manufacture (name, physical address of the manufacturer)

Information from 3.2.S.2 should be included:
Information on the manufacturer.
A brief description of the manufacturing process and the controls.
A flow diagram, as provided in 3.2.S.2.2

2.3. S.3 Control of Drug Substance

A brief summary of the justification of the specification(s), the analytical procedures, and validation should be included.

2.3. S.4 Container Closure System

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

2.3. S.5 Stability

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

shelf-life.

2.3. P Veterinary Pharmaceutical Products

2.3. P.1 Description and Composition of the drug Product

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 (name, physical address of the manufacturer)

Information from 3.2.P.3 should include:-

Information on the manufacturer.

A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.

A flow diagram, as provided under 3.2.P.3.3.

A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

2.3.P.4 Control of Excipients

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

2.3.P.5 Control of Drug Product

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 Container Closure System

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

2.3. P.7 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 for multiple dose containers

A tabulated summary of the stability results from 3.2.P.8.3 should be included

MODULE 3: QUALITY INFORMATION

3.1 Table of Contents of the Quality Part

A table of content of the filed product dossier should be provided

3.2 Body of Data

3.2. S ACTIVE SUBSTANCE(s)

The active substance information can be submitted to EAC in one of the following three options:

- Option 1: Certificate of suitability of the European Pharmacopoeia (CEP); or
- Option 2: Drug master file (DMF); or
- Option 3: Full details as prescribed in module 3 of this guideline.

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 complete copy of the CEP (including any annexes) should be provided in Module 1. The authorization to access to the CEP should be duly filled out by the CEP holder on behalf of the VPP manufacturer or applicant to EAC who refers to the CEP as per the template in **annex VI.**

In addition, a written commitment should be included that the applicant will inform EAC if the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the active substance 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.

- 3.2.S.1.3 General properties - discussions on any additional applicable physicochemical and other relevant active substance properties that are not controlled by the CEP and Ph.Eur. monograph, e.g. solubilities and polymorphs as per guidance in this section.

- 3.2.S.3.1 Elucidation of structure and other characteristics - studies to identify polymorphs (exception: where the CEP specifies a polymorphic form) and particle size distribution, where applicable, as per guidance in this section.

- 3.2.S.4.1 Specification - the specifications of the VPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and

any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.

- 3.2.S.1.2 / 3.1.S.4.3 Analytical procedures and validation – for any tests in addition to those in the CEP and Ph.Eur. monograph.

- 3.2.S.4.4 Batch analysis - results from three batches of at least pilot scale, demonstrating compliance with the VPP manufacturer's active substance specifications.

- 3.2.S.6 Container closure system - specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a re-test period.

- 3.2. S.7 Stability - exception: where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.
  In the case of sterile active substances, data on the sterilization process of the active substance, including validation data, should be included in the PD.

Option 2: Drug Master File (DMF)

Full details of the chemistry, manufacturing process, quality controls during manufacturing and process validation for the active substance may be submitted as a DMF by the active substance manufacturer.

In such cases, the Open part (non-proprietary information) needs to be included in its entirety in the PD as an annex to 3.S.1. In addition, the applicant/VPP manufacturer should complete the following sections in the PD and QOS-PD in full according to the guidance provided unless otherwise indicated in the respective sections:

(a) General information S.1.1 through S.1.3
(b) Manufacture S.2
(c) Manufacturer(s) S.2.1
(d) Description of manufacturing process and process controls S.2.2
(e) Controls of critical steps and intermediates S.2.4
(f) Elucidation of structure and other characteristics S.3.1
(g) Impurities S.3.1
(h) Control of the active substance S.4.1 through S.4.5
(i) Reference standards or materials S.5
(j) Container closure system S.6
(k) Stability S.7.1 through S.7.3

It is the responsibility of the applicant to ensure that the complete DMF (i.e. both the applicant's Open part and the active substance manufacturer's restricted part) is supplied to the directly to the participating country 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 of access should be provided in the Module 1 as per template in **annex V.**

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.

Option 3: Full Details in the Product Dossier

Information on the 3.S.1 Active substance sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the active substance, should be submitted in the PD as outlined in the subsequent sections of this guideline. The QOS should be completed as per Section 3.S of this guideline.

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

Information on the nomenclature of the active substance should be provided. For example:

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

The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labelling information (e.g. Prescribing information leaflet and user information leaflet), labelling).

3.2.S.1.2 Structure

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.
This information should be consistent with that provided in Section 3.S.1.1. For active substances existing as salts, the molecular mass of the free base or acid should also be provided.

3.2.S.1.3 General properties

A list should be provided of physicochemical and other relevant properties of the active substance. This information can be used in developing the specifications, in formulating VPPs and in the testing for release and stability purposes.

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

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

Physical description

The description should include appearance, colour and physical state. Solid forms should be identified as being crystalline or amorphous (see 3.S.3.1 for further information on active substance solid forms).

Solubilities/quantitative aqueous pH solubility profile

The following should be provided for all options for the submission of active substance data.

The solubilities in a number of common solvents should be provided (e.g. water, alcohols, dichloromethane, and acetone).

The solubilities over the physiological pH ranges of the target animals 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.

Polymorphism

The following refers to where specific data should be located in the PD:

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

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

Particle size distribution

The studies performed to identify the particle size distribution of the active substance should be provided in Section 3.S.1.3.2 (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.
Reference documents: ICH Q6A

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

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

The facilities involved in the manufacturing, packaging, labeling, testing and storage of the active substance should be listed. If certain companies are responsible only for specific steps (e.g. milling of the active substance), 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 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 to produce active substances. If available, a certificate of GMP compliance should be provided in the PD in Module 1.

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

The description of the active substance manufacturing process represents the applicant's commitment for the manufacture of the active substance. 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 active substance 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, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or filed in 3.1.S.2.5.

Where the DMF procedure is used, a cross-reference to the restricted part of the DMF may be indicated for confidential information. In this case, if detailed information is presented in the restricted part, the information to be provided for this section of the PD includes a flow chart (including molecular structures and all reagents and solvents) and a brief outline of the manufacturing process, with special emphasis on the final steps including purification procedures. However, for sterile active substances full validation

data on the sterilization process should be provided in the Open part (in cases where there is no further sterilization of the final product).

The following requirements apply to the third option for submission of active substance information, where full details are provided in the dossier.

As discussed in ICH Q7, the point at which the active substance starting material is introduced into the manufacturing process is the starting point of the application of GMP requirements, according to the above guideline. The active substance starting material itself needs to be proposed and justified by the manufacturer and accepted as such by assessors. This justification should be documented and be available for review by EAC GMP inspectors.

The active substance 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 active substance 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.2.3 for further guidance.

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

Where there are multiple manufacturing sites for one active substance 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 polymorphic/amorphous forms have been identified, the form resulting from the synthesis should be stated.

Where particle size is considered a critical attribute (see 3.2.S.3.1 for details), the particle size reduction method(s) (milling, micronization) should be described.

Justification should be provided for alternate manufacturing processes. 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 3.2.S.3.2.

It is acceptable to provide information on pilot scale manufacture, provided it is representative of production scale and scale-up is reported immediately to the RC according to the requirements of the EAC variation guideline.

3.2.S.2.3 Control of Materials

Materials used in the manufacture of the active substance (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, as appropriate.

Where the DMF procedure is used, a cross-reference to the restricted part of the DMF is considered sufficient for this section.

The following requirements apply to the third option for submission of active substance information, where full details are provided in the dossier.

In general, the starting material for synthesis described in the PD should:

- Be a synthetic precursor of one or more synthesis steps prior to the final active substance intermediate. acids, bases, salts, esters and similar derivatives of the active substance, as well as the racemate of a single enantiomer active substance, are not considered final intermediates;

- Be a well characterized, isolated and purified substance with its structure fully elucidated including its stereochemistry (when applicable);

- Have well defined specifications that include among others one or more specific identity tests and tests and limits for assay and specified, unspecified and total impurities;

- Be incorporated as a significant structural fragment into the structure of the active substance.

For each starting material, the name and manufacturing site address of the manufacturer should be indicated. If there are several manufacturers, it should be clarified whether the starting material obtained from different sources is prepared by the same route of synthesis or if different routes are used. Specifications proposed for the starting material should apply to the material from each source.

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 provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material for synthesis should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

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

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

When available, a CEP demonstrating TSE-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module1.
Reference documents: ICH Q6A

3.2.S.2.4 Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled should be provided.

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

Where the DMF procedure is used a cross-reference to the restricted part of the DMF is considered sufficient for this section of the PD, with the exception of information that is also relevant for the applicant

3.2. S.2.5 Process Validation and/or Assessment

Process validation and/or assessment studies for aseptic processing and sterilization should be included.

Where the DMF procedure is used, a cross-reference to the restricted part of the DMF is considered sufficient for this section of the PD.

The following requirements apply to the third option for submission of active substance information, where full details are provided in the dossier.

It is expected that the manufacturing processes for all active substances are properly controlled. If the active substance 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 active substance during storage and transportation should also be provided. Alternate processes should be justified and described (see guidance in 3.2.S.2.2 for the level of detail expected).

3.2.S.2.6 Manufacturing Process Development

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

Where the DMF procedure is used, a cross-reference to the restricted part of the DMF is considered sufficient for this section of the PD.

3.2. S.3 Characterization

3.2. S.3.1 Elucidation of Structure and other Characteristics

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

Elucidation of structure

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 active substance. The QOS-PD should include a list of the studies performed and a conclusion from the studies (e.g. if the results support the proposed structure).

For active substances 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 (XRPD) and differential scanning calorimetry (DSC).

For active substances that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the active substance from each of the proposed manufacturer(s) run concomitantly with a pharmacopoeial reference standard. See Section 3.S.5 for details on acceptable reference standards or materials.

Isomerism/Stereochemistry

When an active substance is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the comparative biostudies, and information should be given as to the stereoisomer of the active substance that is to be used in the VPP.

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 identicality of the isomeric composition of the active substance to that of the active substance 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 active substance specification should include a test to ensure isomeric identity and purity.
The potential for interconversion of the isomers in the isomeric mixture, or racemisation of the single enantiomer should be discussed.

When a single enantiomer of the active substance is claimed for non-pharmacopoeial active substances, unequivocal proof of absolute configuration of asymmetric centers should be provided such as determined by X-ray of a single crystal.
If, based on the structure of the active substance, there is not a potential for stereoisomerism, it is sufficient to include a statement to this effect.

Polymorphism

Many active substances can exist in different physical forms in the solid state. Polymorphism is characterized as the ability of an active substance 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 nonstoichiometric amounts of a solvent. If the incorporated solvent is water, the solvates 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 active substance processability, 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 active substance manufacturers are expected to have adequate knowledge about the polymorphism of the active substances 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. 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 active substance. Demonstration of a nonequivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. XRPD 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]) are helpful to further characterize polymorphic forms. Where polymorphism is a concern, the applicants/manufacturers of active substances should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

Decision tree 4(1) of ICH Q6A can be used where screening is necessary and 4(2) can be used to investigate if different polymorphic forms have different properties that may affect performance, bioavailability and stability of the VPP and to decide whether a preferred polymorph should be monitored at release and on storage of the active substance. Where there is a preferred polymorph, acceptance criteria should be incorporated into the active substance specification to ensure polymorphic equivalence of the commercial

material and that of the active substance batches used in the comparative bioavailability or biowaiver studies. The polymorphic characterization of the active substance batches used in comparative bioavailability or biowaiver studies by the above mentioned methods should be provided. The method used to control polymorphic form should be demonstrated to be specific for the preferred form.

Polymorphism can also include solvation or hydration products (also known as pseudopolymorphs). If the active substance is used in a solvated form, the following information should be provided:

- Specifications for the solvent-free active substance in 3.2.S.2.4, if that compound is a synthetic precursor;
- specifications for the solvated active substance including appropriate limits on the weight ratio of active substance 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 active substances that are not highly soluble contained in solid VPPs, or liquid VPPs containing un-dissolved active substance, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behavior of the VPP. Particle size distribution can also be important in dosage form performance (e.g. delivery of inhalation products), achieving uniformity of content in low-dose tablets (e.g. 2 mg or less), desired smoothness in ophthalmic preparations and stability of suspensions.

If particle size distribution is an important parameter (e.g. as in the above cases), results from an investigation of several batches of the active substance should be provided, including characterization of the batch (es) used in the comparative bioavailability or biowaiver studies. active substance specifications should include controls on the particle size distribution to ensure consistency with the material in the batch(es) used in the comparative bioavailability and biowaiver studies (e.g. limits for d10, d50 and d90). The criteria should be established statistically based on the standard deviation of the test results from the previously mentioned studies. The following is provided for illustrative purposes as possible acceptance criteria for particle size distribution limits:

- d10 not more than (NMT) 10% of total volume less than X 7m
- d50 XX 7m - XXX 7m
- d90 not less than (NLT) 90% of total volume less than XXXX 7m.

Other controls on particle size distribution can be considered acceptable, if scientifically justified.
Reference documents: ICH Q6A

3.2. S.3.2 Impurities

Information on impurities should be provided.
Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A, Q3B and Q3C

impurity guidelines. Additional information to provide further guidance on some of the elements discussed in the ICH guidelines is outlined below.

Regardless of whether a pharmacopoeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture, or degradation of the active substance. 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 pharmacopoeial active substances should not be limited to the impurities specified in the active substance monograph.

The tables in the QOS-PD template should be used to summarize the information on the active substance-related and process-related impurities. In the QOS-PD, the term origin refers to how and where the impurity was introduced (e.g. "Synthetic intermediate from Step 4 of the synthesis", "Potential by-product due to rearrangement from Step 6 of the synthesis"). It should also be indicated if the impurity is a metabolite of the active substance.

The ICH thresholds for reporting, identification (used to set the limit for individual unknown impurities) and qualification are determined on the basis of potential exposure to the impurity, e.g. by the maximum daily dose (MDD) of the active substance. For active substances available in multiple dosage forms and strengths having different MDD values, it is imperative that the thresholds and corresponding controls for each of the presentations be considered to ensure that the risks posed by impurities have been addressed. This is normally achieved by using the highest potential daily MDD, rather than the maintenance dose. For parenteral products, the maximum hourly dose of the active substance should also be included.

It is acknowledged that active substances of semi-synthetic origin do not fall within the scope of the ICH impurity guidelines. However, depending on the nature of the active substance and the extent of the chemical modification steps, the principles on the control of impurities (e.g. reporting, identification and qualification) could also be extended to active substances of semi-synthetic origin. As an illustrative example, an active substance whose precursor molecule was derived from a fermentation process, or a natural product of plant or animal origin that has subsequently undergone several chemical modification reactions generally would fall within this scope, whereas an active substance whose sole chemical step was the formation of a salt from a fermentation product generally would not fall within this scope. It is understood that there is some latitude for these types of active substances.

Identification of impurities

It is recognized by the pharmacopoeias that active substances 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 PD 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 active substances having a maximum

daily dose ≤2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendial monograph that could potentially be higher than the applicable ICH limit.

Qualification of impurities

The ICH impurity guidelines should be consulted for options on the qualification of impurities. The limit specified for an identified impurity in an officially recognized pharmacopoeia is generally considered to be qualified. The following is an additional option for qualification of impurities in existing active substances:

The limit for an impurity present in an existing active substance can be accepted by comparing the impurity results found in the existing active substance with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g. comparative HPLC studies). 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 are not considered acceptable/qualified.
A specified impurity present in the existing active substance is considered qualified if the amount of the impurity in the existing active substance reflects the levels observed in the innovator or VPP.

Basis for setting the acceptance criteria

The basis for setting the acceptance criteria for the impurities should be provided. This is established by considering the identification and qualification thresholds for active substance-related impurities (e.g. starting materials, by-products, intermediates, chiral impurities or degradation products) and the concentration limits for process-related impurities (e.g. residual solvents) as per the applicable ICH guidelines (e.g. Q3A, Q3C).

The qualified level should be considered as the maximum allowable limit. However, limits which are considerably wider than the actual manufacturing process capability are generally discouraged. For this reason, the acceptance criteria are also set taking into consideration the actual levels of impurities found in several batches of the active substance from each manufacturer, including the levels found in the batches used for the comparative bioavailability or biowaiver studies. When reporting the results of quantitative tests, the actual numerical results should be provided rather than vague statements such as “within limits” or“conforms”. In the cases where a large number of batches have been tested it is acceptable to summarize the results of the total number of batches tested with a range of analytical results.

If there are identified impurities specified in an official compendial monograph that are not controlled by the proposed routine in-house analytical procedure, a justification for their exclusion from routine analyses should be provided. If acceptable justification cannot be provided it should be demonstrated that the routine in-house method is capable of separating and detecting the impurities specified in the official compendial monograph

at an acceptable level (e.g. 0.10%). If such a demonstration cannot be performed, a one-time study should be conducted applying the pharmacopoeial method to several recent batches to demonstrate the absence of the pharmacopoeial listed impurities.

For guidance on acceptable residual solvent limits, refer to VICH GL18(R).

The absence of known established highly toxic impurities (genotoxic) used in the process or formed as a by-product should be discussed and suitable limits should be proposed. The limits should be justified by appropriate reference to available guidance or by providing experimental safety data or published data in peer-reviewed journals.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of active substance are to be controlled in specifications. This requirement does not apply to metals that are deliberate components of the pharmaceutical substance (such as a counter ion of a salt) or metals that are used as a pharmaceutical excipient in the VPP (e.g. an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents or any equivalent approaches can be used to address this issue. The requirement normally does not apply to extraneous metal contaminants that are more appropriately addressed by GMP, GDP or any other relevant quality provision such as the heavy metal test in monographs of recognized pharmacopoeias that cover metal contamination originating from manufacturing equipment and the environment.

Reference documents:

- VICH GL10(R) Impurities in New Drug Veterinary Substances

- VICH GL18(R) Impurities: Residual Solvents in a New Veterinary Pharmaceutical product, Active ingredients, excipients http://www.vichsec.org/en/guidelines2.htm

3.2.S.4 Control of the active substance

3.2.S.4.1 Specification

The specification for the active substance should be provided.
As defined in ICH's Q6A guideline, a specification is:
"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."

Copies of the active substance 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 PD, including

specifications from each active substance manufacturer as well as those of the VPP manufacturer.

The VPP manufacturer's active substance specification should be summarized according to the table in the QOS-PD template under the headings tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods).

- The standard declared by the applicant could be an officially recognized compendial standard (e.g. BP, or In 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 (e.g. BP, 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 active substance manufacturer, the VPP manufacturer's active substance 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 active substance 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.
The ICH Q6A guideline outlines recommendations for a number of universal and specific tests and criteria for active substances.
Reference:

ICH, Q6A, officially recognized pharmacopoeia
VICH GL39 — Specifications: Test Procedures and Acceptance Criteria for New
Veterinary Drug Substances and New Pharmaceutical Products:
http://www.vichsec.org/en/guidelines2.htm

3.2.S.4.2 Analytical Procedures

The analytical procedures used for testing the active substance 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 active substance by the VPP manufacturer 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, 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 in-house analytical procedures of the VPP manufacturer for determination of the residual

solvents, assay and purity of the active substance, in section 2.3.S.4.2 of the QOS-PD. 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-PD. Officially recognized compendial methods need not be summarized unless modifications have been made.

Although HPLC is normally considered the method of choice for determining active substance-related impurities, other chromatographic methods such as GC and TLC can also be used, if appropriately validated. For determination of related substances, reference standards should normally be available for each of the identified impurities, particularly those known to be toxic and the concentration of the impurities should be quantified against their own reference standards. Impurity standards may be obtained from pharmacopoeias (individual impurities or resolution mixtures), from commercial sources or prepared in-house. It is considered acceptable to use the active substance as an external standard to estimate the levels of impurities, provided the response factors of those impurities are sufficiently close to that of the active substance, i.e. between 80 and 120%. In cases where the response factor is outside this range, it may still be acceptable to use the active substance, provided a correction factor is applied. Data to support calculation of the correction factor should be provided for an in- house method. Unspecified impurities may be quantified using a solution of the active substance as the reference standard at a concentration corresponding to the limit established for individual unspecified impurities (e.g. 0.10%).

The system suitability tests (SSTs) represent an integral part of the method and are used to ensure the adequate performance of the chosen chromatographic system. As a minimum, HPLC and GC purity methods should include SSTs for resolution and repeatability. For HPLC methods to control active substance-related impurities, this is typically done using a solution of the active substance with a concentration corresponding to the limit for unspecified impurities. Resolution of the two closest eluting peaks is generally recommended. However, the choice of alternate peaks can be used if justified (e.g. choice of a toxic impurity).

3.2. S.4.3 Validation of Analytical Procedures

Analytical validation information, including experimental data for the analytical procedures used for testing the active substance, 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 active substance by the VPP manufacturer, 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 (i.e. 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures of the VPP manufacturer for determination of residual solvents, assay and purity of the active substance, 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.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of comp endial methods can be necessary. The compendial methods as published are typically validated based on an active substance or an VPP originating from a specific manufacturer. Different sources of the same active substance or VPP 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 active substance from the intended source(s).

In general verification is not necessary for compendial active substance 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 active substance-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 active substance spiked with impurities at concentrations equivalent to their specification limits.
References:
VICH GL1 Text on Validation of Analytical Procedures

VICH GL2 Validation of Analytical Procedures: Methodology
http://www.vichse.org/en/guidelines2.htm

3.2. S.4.4 Batch Analyses

Description of batches and results of batch analyses should be provided.

The information provided should include batch number, batch size, date and production site of relevant active substance batches used in comparative bioavailability or biowaiver studies, preclinical and clinical data (if relevant), stability, pilot, scale-up and, if available, production-scale batches. This data is used to establish the specifications and evaluate consistency in active substance quality.

Analytical results should be provided from at least two batches of at least pilot scale from each proposed manufacturing site of the active substance and should include the batch(es) used in the comparative bioavailability or biowaiver studies. A pilot-scale batch should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

Copies of the certificates of analysis, both from the active substance manufacturer(s) and the VPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. The VPP manufacturer's test results should be summarized in the QOS-PD.

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

3.2. S.4.5 Justification of Specification

Justification for the active substance 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.

3.2.S.5 Reference Standards or Materials

Information on the reference standards or reference materials used for testing of the active substance 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 VPP manufacturer in routine active substance and VPP testing.

The source(s) of the reference standards or materials used in the testing of the active substance should be provided (e.g. those used for the identification, purity, assay tests). These could be classified as primary or secondary reference standards.

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (e.g. Ph.Eur., BP,) where one exists and the lot number should be provided. Where a pharmacopoeial standard is claimed for the active substance and/or the VPP, the primary reference standard should be obtained from that pharmacopoeia when available. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise, a primary standard may be a batch of the active substance 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).

Reference standards should normally be established for specified impurities. Refer to section 3.2.S.4.2 for additional guidance

Reference documents: ICH Q6A,

3.2.S.6 Container Closure System

A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-Compendial methods (with validation) should be included, where appropriate. For non-functional secondary packaging components (e.g., those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the active substance, including adsorption to container and leaching, and/or safety of materials of construction.

Primary packaging components are those that are in direct contact with the active substance or 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 active substance should be provided and should include the conditions of storage. In addition, the name and address of the manufacturer of the active substance should be stated on the container, regardless of whether relabeling is conducted at any stage during the active substance distribution process.

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

The types of studies conducted, protocols used, and the results of the studies should be summarised. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and re-test date or shelf-life, as appropriate. The purpose of stability testing is to:

> "Provide evidence of how the quality of an active substance or VPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light."

The tables in the QOS-PD template should be used to summarize the results from the stability studies and related information (e.g. conditions, testing parameters, conclusions, commitments).

Stress testing

Publications from peer-reviewed literature could be submitted to support/replace experimental data
Stress testing of the active substance can help to identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual active substance and the type of VPP involved.

Degradation paths for pharmaceutical compounds are typically reactions of hydrolysis, oxidation, photolysis, and/or acid-base chemistry. To force these reactions, the active substance or VPP is placed in solution expediently, for example, under the conditions shown in the following table.

Stress factor	Conditions
Heat	60°C
Humidity	75% RH or greater
Acid	0.1N HCl
Base	0.1N NaOH
Oxidative	3% H_2O_2

Photolytic	Metal halide, Hg Xe lamp, or UV-B/fluorescent
Metal ions (optional)	0.05 M Fe2+ or Cu2+

The objective is not to completely degrade the active compound but to generate degradation to a small extent, typically 10-30% loss of active by assay when compared with non-degraded compound. This target is chosen so that some degradation occurs, but it is not so severe that secondary products are generated. (Secondary degradation products are degradation products of degradation products and in most cases are not observed during stability studies.) In the total absence of degradation products after 10 days, the active substance is considered stable. If degradation is detectable but its extent is less than 10%, then the stress factors or the stress conditions, or both, should be increased.

Stress testing is to be carried out on a single batch of the active substance. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in VICH GL5.

Solid-state degradation can also be considered. For active substances, placing a solid sample at elevated temperatures —e.g., 60-120 °C, or 5-10 °C below the melting point— can generate some degradation compounds. Because of the harsher conditions, these compounds may not be observed under the accelerated stress studies. However, this approach serves to generate degradation products that can be used as a worst case to assess the analytical method performance.

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

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

- When available, it is acceptable to provide the relevant data published in the “peer review” literature to support the proposed degradation pathways.

- When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to EAC.

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

Accelerated and long-term testing

Summarize the stability testing program and report the results of stability testing of not less than three (minimum one production scale and two pilot scale) batches of the active substance. The data for each attribute should be discussed, trends analyzed and a re-test date should be proposed. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the dossier, a cross-reference will suffice. If different methodology was used, provide validation of tests for impurities including degradants and assay and for other tests as necessary. At the time of submitting the dossier, the general requirements are:

Storage temperature (°C)	Relative humidity (%)	Minimum time period covered by data at submission (months)
Accelerated: 40±2	75±5	6
Long term: 30±2	75±5	12
Long term: 25±2 Long term:30±2 –	60±5 65±5	12 12

Note:
A storage statement should be proposed for the labeling (if applicable), which should be based on the stability assessment of the active substance.

A re-test period should be derived from the stability information, and the approved re-test date should be displayed on the container label and CoA. Unless otherwise justified, the long-term stability studies should be conducted at 30°C ± 2°C/75± 5% RH conditions.

3.2.S.7.2 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 re-test 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 pharmaceutical products,

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

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

3.2. P.1 Description and Composition of the VPP

Information provided should include:

3.2.P.1.1 Description of the dosage form

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

3.2.P.1.2 Composition

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

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

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

The components should be declared by their proper or common names, quality standards (e.g. BP, House) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilised, emulsified).

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

The qualitative composition, including solvents, should be provided for all proprietary components or blends (e.g. capsule shells, colouring blends, imprinting inks). This information (excluding the solvents) is to be listed in the product information (e.g. prescribing information leaflet, User information leaflet and labelling).

3.2.P.1.3 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 EAC, 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 EAC, information on the diluent(s) should be provided in a separate VPP portion ("3.2.P"), as appropriate.

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/Aluminum foil unit dose blisters (in packages of 2's (blister of 2 x1, 10 blisters per package)."

Reference documents: ICH Q6A

3.2.P.2 Pharmaceutical Development

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

Pharmaceutical development information should include, at a minimum:

- 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;

- 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;

- 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;

Discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner. These features should be discussed as part of the product development using the principles of risk management over the entire lifecycle of the product (ref: ICH Q8).

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

References:

- ICH Q6A guidelines
- ICH Q8 guidelines: Pharmaceutical Development
- ICH Q9 guidelines: Quality Risk Management
- ICH Q10 guidelines

3.2.P.2.1 Components of the VPP

3.2.P.2.1.1 Active substance

The compatibility of the active substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristics (e.g., water content, solubility, and particle size distribution, polymorphic or solid state form) of the active substance that can influence the performance of the VPP should be discussed. For fixed-dose combinations, the compatibility of active substances with each other should be discussed.

Physicochemical characteristics of the active substance may influence both the manufacturing capability and the performance of the VPP.

In addition to visual examination, chromatographic results (assay, purity) are required to demonstrate active substance-active substance and active substance-excipient compatibility. In general, active substance-excipient compatibility is not required to be established for specific excipients when evidence is provided (e.g. Prescribing information leaflet) that the excipients are present in the comparator product.

3.2. P.2.1.2 Excipients

The choice of excipients listed in 3.2.P.1, their concentration, and their characteristics that can influence the VPP performance should be discussed relative to their respective functions.

Ranges or alternates for excipients are normally not accepted, unless supported by appropriate process validation data. Where relevant, compatibility study results (e.g. compatibility of a primary or secondary amine active substance with lactose) should be included to justify the choice

of excipients. Specific details should be provided where necessary (e.g. use of potato or corn starch).
Where antioxidants are included in the formulation, the effectiveness of the proposed concentration of the antioxidant should be justified and verified by appropriate studies.
Antimicrobial preservatives are discussed in 3.2.P.2.5.

3.2. P.2.2 Finished Pharmaceutical Product

3.2. P.2.2.1 Formulation Development

A brief summary describing the development of the VPP should be provided, taking into consideration the proposed route of administration and usage. The differences between the comparative bioavailability or biowaiver formulations and the formulation (i.e., composition) described in 3.2.P.1 should be discussed. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed, when appropriate.

An established generic product as one that has been marketed by the applicant or manufacturer associated with the dossier for at least five years and for which at least 10 production batches were produced over the previous year, or, if less than 10 batches were produced in the previous year, not less than 25 batches were produced in the previous three years. For products that meet the criteria of an established generic product, all sections of 3.2.P.2.1 of the dossier and QOS-PD should be completed with the exception of 3.2.P.2.1 (a). In addition, a product quality review should be provided as outlined in **Annex IV**

If the proposed VPP is a scored tablet, the results of a study should be provided of the uniformity of dosage units of the tablet halves. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity or weight variation, depending on the requirement for the whole tablet) should be performed on each split portion from a minimum of 10 randomly selected whole tablets. As an illustrative example, the number of units (i.e. the splits) would be 10 halves for bisected tablets (one half of each tablet is retained for the test) or 10 quarters for quadrisect tablets (one quarter of each tablet is retained for the test). At least one batch of each strength should be tested. Ideally, the study should cover a range of the hardness values. The splitting of the tablets should be performed in a manner that would be representative of that used by the consumer (e.g. manually split by hand). The uniformity test on split portions can be demonstrated on a one-time basis and does not need to be added to the VPP specification(s). The tablet description in the VPP specification and in the product information (e.g. prescribing information leaflet and user information leaflet, and labeling,) should reflect the presence of a score.

In vitro dissolution or drug release

A discussion should be included as to how the development of the formulation relates to development of the dissolution method(s) and the generation of the dissolution profile.

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed, medium) should be provided. Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the pharmacokinetic parameters. Use of a single point test or a dissolution range should be justified based on the solubility of the active substance.

For slower dissolving immediate-release products (e.g. Q=80% in 90 minutes), a second time point may be warranted (e.g. Q=60% in 45 minutes).

Modified-release VPPs should have a meaningful in vitro release rate (dissolution) test that is used for routine quality control. Preferably this test should possess in vitro-in vivo correlation. Results demonstrating the effect of pH on the dissolution profile should be submitted if appropriate for the type of dosage form.

For extended-release VPPs, the testing conditions should be set to cover the entire time period of expected release (e.g. at least three test intervals chosen for a 12-hour release and additional test intervals for longer duration of release). One of the test points should be at the early stage of drug release (e.g. within the first hour) to demonstrate absence of dose dumping. At each test period, upper and lower limits should be set for individual units. Generally, the acceptance range at each intermediate test point should not exceed 25% or ±12.5% of the targeted value. Dissolution results should be submitted for several lots, including those lots used for pharmacokinetic and bioavailability or biowaiver studies.

3.2.P.2.2.2 Overages

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

3.2.P.2.2.3 Physicochemical and Biological Properties

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

3.2.P.2.3 Manufacturing Process Development

The selection and optimization of the manufacturing process described in 3.2.P.3.3, in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Where relevant, justification for the selection of aseptic processing or other sterilization methods over terminal sterilization should be provided.

Differences between the manufacturing 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.

For products that meet the criteria of an established generic product, in order to fulfill the requirements of section P.2.3 section P.2.3 (b) of the dossier and QOS-PD should be completed and a product quality review should be submitted as outlined in **Annex IV.** The guidance that follows applies to all other products, for which section P.2.3 should be completed in its entirety.

The rationale for choosing the particular pharmaceutical product (e.g. dosage form, delivery system) should be provided. The scientific rationale for the choice of the manufacturing, filling and packaging processes that can influence VPP quality and performance should be explained (e.g. wet granulation using high shear granulator). Active substance stress study results may be included in the rationale. Any developmental work undertaken to protect the VPP from deterioration should also be included (e.g. protection from light or moisture).

The scientific rationale for the selection, optimization and scale-up of the manufacturing process described in 3.2.P.3.3 should be explained; in particular the critical aspects (e.g. rate of addition of granulating fluid, massing time, granulation end-point). A discussion of the critical process parameters (CPP), controls and robustness with respect to the QTPP and CQA of the product should be included (ref: ICH Q8).

3.2.P.2.4 Container Closure System

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

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

3.2.P.2.5 Microbiological Attributes

Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.
Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. Ph.Eur. general chapters on antimicrobial preservatives) using a batch of the VPP. If the lower bound for the proposed acceptance criteria for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the VPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria. A single primary stability batch of the VPP should be tested for effectiveness of the antimicrobial preservative (in addition to preservative content) at the proposed shelf-life for verification purposes, regardless of whether there is a difference between the release and shelf-life acceptance criteria for preservative content.

3.2.P.2.6 Compatibility

The compatibility of the VPP with reconstitution diluent(s) or dosage devices (e.g., precipitation of active substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

Where sterile, reconstituted products are to be further diluted, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labeling. These studies should preferably be conducted on aged samples. Where the labeling does not specify the type of containers, compatibility (with respect to parameters such as appearance, pH, assay, levels of individual and total degradation products, sub visible particulate matter and extractable from the packaging components) should be demonstrated in glass, PVC and polyolefin containers. However, if one or more containers are identified in the labeling, compatibility of admixtures needs to be demonstrated only in the specified containers.

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

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

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

The facilities involved in the manufacturing, packaging, labeling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate), this should be clearly indicated.

The list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

For a mixture of an active substance with an excipient, the blending of the active substance with the excipient is considered to be the first step in the manufacture of the final product and therefore the mixture does not fall under the definition of an active substance. The only exceptions are in the cases where the active substance cannot exist on its own. Similarly, for a mixture of active substances, the blending of the active substances is considered to be the first step in the manufacture of the final product. Sites for such manufacturing steps should be included in this section.

A valid Certificate of Pharmaceutical Product should be submitted to demonstrate that the product is registered or licensed in accordance with national requirements (Module 1).

For each site where the major production step(s) are carried out, when applicable, attach a valid GMP Certificate issued by the competent authority (Module 1).

When there are differences between the product for which this application is submitted and that marketed in the country/countries which provided the WHO-type certificate(s), provide data to support the applicability of the certificate(s) despite the differences. Depending on the case, it may be necessary to provide validation data for differences in site of manufacture, specifications, formulation, etc. Note that only minor differences are likely to be acceptable. Differences in container labeling need not normally be justified.

Regulatory situation in other countries

The countries should be listed in which this product has been granted a marketing authorization, this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn (Module 1).

3.2.P.3.2 Batch Formula

A batch formula should be provided that includes a list of all components of the dosage form to be used in the manufacturing process, their amounts on

a per batch basis, including overages, and a reference to their quality standards.

The tables in the QOS-PD template should be used to summarize the batch formula of the VPP for each proposed commercial batch size and express the quantity of each component on a per batch basis, including a statement of the total weight or measure of the batch.

All components used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the VPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 kg of active ingredient base = 1.065 kg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "Contains 7 kg (corresponding to 2%) overage of the active substance to compensate for manufacturing losses").

The components should be declared by their proper or common names, quality standards (e.g. BP, In-House) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilised, emulsified).

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

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

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

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

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

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.P.2.3.3).

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

For the manufacture of sterile products, the class (e.g. A, B, C etc.) of the areas should be stated for each activity (e.g. compounding, filling, sealing etc), as well as the sterilization parameters for equipment, container/closure, terminal sterilization etc.
Reference documents: ICH Q8, Q9, Q10

3.2.P.3.4 Controls of Critical Steps and Intermediates

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

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

Examples of applicable in-process controls include:

- Granulations: moisture (limits expressed as a range), blend uniformity (e.g. low dose tablets), bulk and tapped densities, particle size distribution;
- Solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;
- Liquids: pH, specific gravity, clarity of solutions; and
- Parenterals: appearance, clarity, fills volume/weight, pH, filter integrity tests, particulate matter, and leak testing of ampoules.

Reference documents:
VICH GL1, VICH GL2
ICH Q6A, Q8, Q9, Q10,

3.2. P.3.5 Process Validation and/or Assessment

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

For products that meet the criteria of an established generic product, a product quality review as outlined in **Annex IV** 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 EAC 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.

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

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, sub visual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

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

The process validation protocol should include inter alia the following:

- a reference to the current master production document;
- 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:

- Washing, treatment, sterilizing and depyrogenating of containers, closures and equipment;
- Filtration of solutions;
- Lyophilization process;
- Leaker test of filled and sealed ampoules;
- Final inspection of the product; and
- 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 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,

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

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

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

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

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

For oils of plant origin (e.g. soy bean oil, peanut oil) the absence of aflatoxins or biocides should be demonstrated.

The colours permitted for use are limited to those listed in the "Japanese pharmaceutical excipients", the EU "List of permitted food colours", and the FDA "Inactive ingredient guide". For proprietary mixtures, the supplier's product sheet with the qualitative formulation should be submitted, in addition to the VPP manufacturer's specifications for the product including identification testing.

For flavours the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. USA or EU).

If additional purification is undertaken on commercially available excipients details of the process of purification and modified specifications should be submitted.

Reference documents:

- ICH Q6A
- List of permitted food colours, Official journal of the European Communities, 1994. L237. (European Commission Directive 94/36/EC).
- Inactive ingredient guide. Rockville, MD, United States Food and Drug Administration, Division of Drug Information and Research, 1996.
- Japanese pharmaceutical excipients. Tokyo, Pharmaceutical and Cosmetics Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (updated annually or biennially).

3.2.P.4.2 Analytical Procedures

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

3.2.P.4.3 Validation of Analytical Procedures

Analytical 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:
VICH GL1 Text on Validation of Analytical Procedures

VICH GL2 Validation of Analytical Procedures: Methodology
http://www.vichse.org/en/guidelines2.htm

3.2. P.4.4 Justification of Specifications

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

3.2.P.4.5 Excipients of Animal Origin

For excipients of animal origin, information should be provided regarding adventitious agents (e.g., sources, specifications, description of the testing performed, viral safety data).

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If from plant origin a declaration to this effect will suffice.

For these excipients from animal origin, evidence or proof confirming that the excipients used to manufacture the VPP are without risk of transmitting agents of animal spongiform encephalopathies.

Materials of animal origin should be avoided whenever possible.

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

Reference documents: ICH Q5A, Q5D, Q6B,

3.2.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.

3.2.P.5 Control of VPP

3.2.P.5.1 Specification(s)

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

"a 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."

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. 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:

a) 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;

b) Modified-release products: a meaningful active substance release method;

c) Suppositories: uniformity of dosage units, melting point;

Unless there is appropriate justification, the acceptable limit for the active substance content of the VPP in the release specifications is ± 5% of the label claim (i.e. 95.0-105.0%).

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

Reference documents:
- VICH GL39 — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Pharmaceutical Products: Chemical Substances + Decision trees.
- ICH Q3B, Q3C, Q6A

3.2.P.5.2 Analytical Procedures

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

as those proposed for routine testing should be provided. Provide copies of compendial analytical procedures used.

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods) can be found in the 2.3.R Regional information section of the QOS (i.e. 2.3.R.2). These tables should be used to summarize the analytical procedures used for determination of the assay, related substances and dissolution of the VPP.

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

3.2. P.5.3 Validation of Analytical Procedures

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

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

Tables for summarizing a number of the different analytical procedures and validation information (e.g. HPLC assay/impurity methods, GC methods) can be found in the 2.3.R Regional information section of the QOS-PD (i.e. 2.3.R.2). These tables should be used to summarize the validation information of the analytical procedures used for determination of the assay, related substances and dissolution of the VPP.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods, as published, are typically validated based on an active substance or an 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.

Reference documents:

- VICH GL1 Text on Validation of Analytical Procedures
- VICH GL2 Validation of Analytical Procedures: Methodology
- ICH Q2
- WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials

3.2.P.5.4 Batch Analyses

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

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

The testing results should include the batch(es) used in the comparative bioavailability or biowaiver studies. Copies of the certificates of analysis for these batches should be provided in the PD and the company responsible for generating the testing results should be identified.

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

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

3.2.P.5.5 Characterisation of Impurities

Information on the characterisation of impurities should be provided, if not previously provided in "3.2.S.3.2 Impurities".

A discussion should be provided 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

3.2.P.5.6 Justification of Specification(s)

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

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

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

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

3.2. P.6 Reference Standards or Materials

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

Reference documents: ICH Q6A

3.2.P.7 Container Closure System

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

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).

3.2.P.8 Stability Testing

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include, for example, conclusions with respect to storage conditions and shelf-life, and, if applicable, in-use storage conditions and shelf-life

The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the active substance and the dosage form.

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

Stability studies should be performed on each individual strength and container size of the finished product unless bracketing or matrixing is applied.

Other supporting data can be provided.

3.2.P.8.1 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 the EAC region.
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.

3.2.P.8.2 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 Pharmaceutical Products
http://www.vichse.org/en/guidelines2.htm

3.2.P.8.3 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.

3.2.P.8.4 Container Closure System

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

3.2.P.8.5 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 Pharmaceutical product

http://www.vichse.org/en/guidelines2.htm

3.2.P.8.6 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 RC.

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).

3.2. P.8.7 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	12

Note. Unless otherwise justified, 30°C ± 2°C/75% RH ± 5% RH is the long term stability condition for products to be marketed in Tanzania.

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

In general, “significant change” for a finished product is defined as:

- A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures.
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., colour, phase separation, hardness).
- And, as appropriate for the dosage form:
  - Failure to meet the acceptance criterion for pH; or
  - Failure to meet the acceptance criteria for dissolution for 12 dosage units.

3.2.P.8.8 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.

3.2.P.8.9 Finished products packaged in semi-permeable containers

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

Study	Storage condition	Minimum time period covered by data at submission (months)
Long term	30±2°C/75±5% RH	12
Accelerated	40±2°C/NMT 25±5% RH	6

Note. Unless otherwise justified, 30 ± 2°C and 75 ± 5% RH is the long term stability condition for products to be marketed in the EAC region.
Ultimately, it should be demonstrated that aqueous-based finished products stored in semi-permeable containers could withstand low relative humidity environments. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

A 5% loss in water from its initial value is considered a significant change for a VPP packaged in a semi-permeable container after three (3) months storage at 40 ± 2°C and NMT 25 ± 5% RH.

3.2.P.8.10 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

3.2.P.8.11 Extrapolation of data

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

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

- VICH-GL3 Assessment For Stability Data

Core Storage Statements

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

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

Drug product intended for storage in a refrigerator

Study	Storage condition	Minimum time period covered by data at submission
Long term	5°C±3°C	12 months
Accelerated	25°C±2°C/60%RH±5% RH	6 moths

3.3. R .REGIONAL INFORMATION

3.3. R.1 Production Documentation

3.3. R.1.1 Executed Production Documents for commercial batch size

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

3.3. R.1.2 Master Production Documents

(a) The blank master production documents,

3.3.R.2 Analytical Procedures and Validation Information

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES

ATTACHMENT NUMBER/NAME:	

HPLC Method Summary		**Volume/Page:**	
Method name:			
Method code:		**Version and/or Date:**	
Column(s) / temperature (if other than ambient):			
Mobile phase (specify gradient program, if applicable):			
Detector (and wavelength, if applicable):			
Flow rate:			
Injection volume:			
Sample solution concentration (expressed as mg/ml, let this be termed "A"):			
Reference solution concentration (expressed as mg/ml and as % of "A"):			
System suitability solution concentration (expressed as mg/ml and as % of "A"):			
System suitability tests (tests and acceptance criteria):			
Method of quantification (e.g. against ACTIVE SUBSTANCE or impurity reference standard(s)):			
Other information (specify):			

ATTACHMENT NUMBER/NAME:	

Validation Summary	**Volume/Page:**			
Analytes:				
Typical retention times (RT)				
Relative retention times ($RT_{Imp.}/RT_{ACTIVE\ SUBSTANCE\ or\ Int.\ Std.}$):				
Relative response factor ($RF_{Imp.}/RF_{ACTIVE\ SUBSTANCE}$):				

ATTACHMENT NUMBER/NAME:					
Specificity:					
Linearity / Range:	Number of concentrations: Range (expressed as % "A"): Slope: Y-intercept: Correlation coefficient (r^2) :				
Accuracy:	Conc.(s) (expressed as % "A"): Number of replicates: Percent recovery (avg/RSD):				
Precision / Repeatability: (intra-assay precision)	Conc.(s) (expressed as % "A"): Number of replicates: Result (avg/RSD):				
Precision / Intermediate Precision: (days/analysts/equipment)	Parameter(s) altered: Result (avg/RSD):				
Limit of Detection (LOD): (expressed as % "A")					
Limit of Quantitation (LOQ): (expressed as % "A")					
Robustness:	Stability of solutions: Other variables/effects:				
Typical chromatograms or spectra may be found in:					
Company(s) responsible for method validation:					
Other information (specify):					

MODULE 4: NON-CLINICAL STUDY REPORTS

4.1 Table of contents of module

4.2 Body data

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

The objective of non clinical studies is to define the pharmacological actions (Pharmacodynamic and pharmacokinetics) and toxicological effects of the active substance in test animals and target species, users, consumers and the environments. This normally involves initial studies in laboratory animals and later on pre-clinical studies in the target species, which should take into consideration the following:

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

The safety documentation of the dossier shall show:

(a) The potential toxicity of the veterinary medicine and any dangerous effects which may occur under the proposed conditions of use in animals. These should be evaluated in relation to the severity of the pathological condition concerned;
(b) The potential harmful effects to man of residues of the veterinary medicine or substance in foodstuffs obtained from treated animals and what difficulties these residues may create in the industrial processing of foodstuff;
(c) The potential risks which may result from the exposure of veterinary beings to the 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 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

4.2.1 Pharmacological studies

4.2.1.1 Pharmacodynamics

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

4.2.1.1.1 Other actions (desired/undesired)

Give assessment summary of action(s) other than those of therapeutic use. The results of two or three dosage levels studied should be submitted, with the lowest level representing the ED_{50} for the active substance's primary action on the animal species being investigated.

For effects, which may be expected to have significant adverse reactions, attempts should be made to estimate the threshold levels.

4.2.1.1.2 Pharmacodynamic interactions

The applicant shall submit data either to establish that such interactions do not occur or that they are clearly recognized and defined.

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

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

4.2.1.2 Pharmacokinetics

Pharmacokinetics studies should be made with single dose by various routes. Repeated dose studies should also be performed when relevant, to establish the pharmacokinetics of chronic drug administration.

Metabolic studies should be conducted on species used in toxicological and reproduction studies using the proposed clinical routes of administration.

Where radioactive labelled materials are used in studies, position of label stability and specificity of material should be stated.

Where the product contains a combination of drugs, the effect of use of two or more drugs on the pharmacokinetics of one or the other drugs should be established.

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

4.2.1.2.1 Absorption

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

4.2.1.2.2 Distribution of active substance and metabolites

Provide a summary and time course of distribution of the active substance and metabolites in body fluids, tissues, and organs.

Accumulation, retention of the drug/metabolites in tissues, organs, penetration of blood-brain and placental barriers, plasma binding all these parameters should be reported in quantitative form.

4.2.1.2.3 Biotransformation

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

4.2.1.2.4 Pharmacokinetic interactions

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

4.2.1.2.5 Excretion

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

4.2.1.3 Toxicological studies

The scope of toxicological assessment should be described in relation to the proposed clinical use. Information obtained from experimental and biological studies of all aspects of toxicology (general toxicity, acute toxicity studies, sub-acute toxicity and long term toxicity studies including teratology, reproduction effects, carcinogenicity, genotoxicity, immunogenicity, microbial affects (e.g. development of resistance), local tolerance (potential for adverse effects at site of administration, etc) is required to establish the safe use of the drug and must be submitted for all new drug applications.

The investigation should, if possible, include experiments conducted with the drug in the vehicle intended for therapeutic application or its final pharmaceutical formulation (product).

4.2.1.3.1 General Toxicity Studies

In general toxicity studies, at least three or more routes of administration should be used including one for therapeutic use and at least one other which ensures systemic absorption, i.e. intravenous, intramuscular or subcutaneous.

Different dose levels spaced logarithmically should be used. The maximum tolerated dose should be indicated.

All animals dying during the experiment should be autopsied and cause of death determined where possible.

Full post-mortem should be carried out on all animals and histopathological studies undertaken on control and dosed groups.

Results should be tabulated. Full data for all parameters measured, with mean, range for groups, should be included.

If it is expected that the product will be used in young animals, studies should be conducted on both adult and young animals.

4.2.1.3.2 Acute toxicity studies

Principles governing general toxicity studies shall be applicable to acute, sub-acute and long term toxicity studies and local tolerability studies

LD_{50}

Single-dose toxicity studies can be used to:

(a) Predict the possible effects of acute overdosing in the target species;
(b) Predict the possible effects of accidental administration to veterinaries;
(c) Predict the doses which may usefully be employed in the repeat dose studies
(d) Assess the relative toxicity of the compound.

Single dose toxicity studies should reveal the acute toxic effects of the substances and the time course for their onset and remission. These studies should normally be carried out in both sexes of at least two mammalian species. One species may be replaced, if appropriate, by an animal species for which the 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 pharmaceutical product is anticipated, for example for inhalation or dermal contact, these routes should be studied.

4.2.1.3.3 Sub acute toxicity studies

Repeat-dose toxicity tests are intended to reveal any physiological and/or pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

In the case of substances or pharmaceutical products intended solely for use in animals which do not produce food for human consumption, a repeat- dose toxicity study in one species of experimental animal will normally be

sufficient. This study may be replaced by a study conducted in the target species. The frequency and route of administration, and the duration of the study should be chosen having regard to the proposed conditions of clinical use. The investigator shall give reasons for the extent and duration of the trials and the dosages chosen.

In the case of substances or pharmaceutical products intended for use in food producing animals, the studies should be conducted in at least two species, one of which should be a non-rodent. The investigator shall give reasons for the choice of species, having regard to the available knowledge of the metabolism of the product in animals and man. The test substance shall be administered orally. The duration of some of the studies shall be at least 90 days. The investigator shall clearly state and give reasons for the method and frequency of administration and the length of the trials.

The maximum dose should normally be selected so as to bring harmful effects to light. The lowest dose level should not produce any evidence of toxicity.

Assessment of the toxic effects shall be based on observation of behaviour, growth, haematology and physiological tests, especially those relating to the excretory organs, and also autopsy reports and accompanying histological data. The choice and range of each group of tests depends on the species of animal used and the state of scientific knowledge at the time.

References

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

4.2.1.3.4 Long term toxicity studies

Where applicable long-term toxicity determinations i.e. one year chronic study in dogs or a lifetime chronic study in rats, may be required.
Long-term animal carcinogenicity studies will usually be required for substances to:

(a) Which veterinary beings will be exposed,
(b) Which have a close chemical analogy with known carcinogens,
(c) Which during mutagenicity testing produced results indicate a possibility of carcinogenic effects
(d) Which gave rise to suspect signs during toxicity testing

The state of scientific knowledge at the time the application is submitted shall be taken into account when designing carcinogenicity studies and evaluating their results

References:

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

4.2.1.3.4.1 Mutagenicity/Clastogenicity

Mutagenicity tests are intended to assess the potential of substances to cause transmissible changes in the genetic material of cells. If there is any indication of mutagenicity, carcinogenicity studies will be required.

Any new substances intended for use in veterinary pharmaceutical products must be assessed for mutagenic properties.

The number and types of tests and the criteria for the assessment of the results shall depend on the state of scientific knowledge when the application is submitted.

References;

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

4.2.1.3.4.2 Reproductive toxicity studies

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

The purpose of such studies is to identify possible impairment of male or female reproductive function or harmful effects on progeny resulting from the administration of the pharmaceutical products or substance under investigation.

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.

4.2.1.3.4.3 Study of embryotoxic/foetotoxic effects including teratogenicity

Embryotoxic/foetotoxic, including teratogenicity studies will be required:

In the case of substances or pharmaceutical products intended for use in food-producing animals, studies of embryotoxic/foetotoxic effects, including teratogenicity, shall be carried out. These studies shall be carried out in at least two mammalian species, usually a rodent and the rabbit. The details of the test (number of animals, doses, time at which administered and criteria for the assessment of results) shall depend on the state of scientific

knowledge at the time the application is lodged and the level of statistical significance which the results should attain. The rodent study may be combined with the study of effects on reproductive function.

In the case of substances or pharmaceutical products which are not intended for use in food-producing animals, to animals which might be used for breeding, a study of embryotoxic/fetotoxic effects, including teratogenicity, shall be required in at least one species, which may be the target species

4.2.1.3.4.4 Neurotoxicity

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

4.2.1.3.4.5 Immunotoxicity

Where the effects observed during repeated dose studies in animals reveal specific changes in lymphoid organ weights and/or histology and/or changes in the cellularity of lymphoid tissues, bone marrow or peripheral leukocytes, the investigator shall consider the need for additional studies of the effects of the product on the immune system.

The state of scientific knowledge at the time the application to be is submitted shall be taken into account when designing such studies and evaluating their results.

Reference

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

4.2.1.4 Safety to users

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

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

Residue study data from pharmacokinetic/tissue residue depletion studies should be provided to justify withdrawal periods for milk, meat, eggs for each species for which the product is indicated.

Safety assessment of veterinary drugs residues in food of animal origin should be performed for all new drugs. Relevant pharmacological, toxicological, microbiological end points should be used to establish acceptable daily intake. Maximum residue limits in food producing animals

should be provided. All the analytical methods used should be provided.

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

References

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

4.2.1.6 Toxicity to the environment

Requirements for safety are important to avoid persistent damage to the environment. An assessment of the potential of exposure of the drug and its active metabolites to the environment shall be made taking into account:

(a) The target species and likelihood of and method of excretion of the product and its active metabolites into the environment.
(b) Pattern of use and therefore quantity drug to be used (herd/flock medication or individual medication)
(c) The method of administration and whether it may lead to direct entry of the product into the environment, e.g. sprays
(d) The method of disposal of the unused, used products and containers

Studies on potential harmful effect of the product to the environment shall be provided. The environment shall include soil, water and air such studies shall include:

(a) Fate and behaviour in the soil
(b) Effects on soil organisms
(c) Fate and behaviour in water
(d) Effect on aquatic organisms
(e) Effects of other non-target organisms

Proposed measures to minimize the above potential risks during use of the product shall be described.

Data on environmental safety assessment shall be given for the following products:

(a) Antibiotics in poultry, pig and fish feeds
(b) Antihelmintics in large animals e.g. invermectins
(c) Expired drugs from the market
(d) Effluents from manufacturing plants
(e) Hazardous or potentially hazardous non pharmaceutical materials (used devices e.g. needles, syringes and gloves)
(e) External preparations

Reference

- VICH GL6 (Ecotoxicity - Phase 1) Environmental Impact Assessment (EIAs) for veterinary pharmaceutical products (VPPs) - Phase 1

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

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

MODULE 5: CLINICAL STUDY REPORTS

5.1 Interchangeability

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

(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 cross-over design is preferred and where it is not appropriate a parallel design is acceptable. The study design must consider the pathology and natural history of the condition.

(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 Laboratory Practice (GLP) should be adhered to during the study.

(vii) Where possible the effect can be graphically illustrated using the area under the effect time curve, maximum effect and time of maximum effect.

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

- The response can be measured precisely over a reasonable range

- The response can be measured repeatedly to obtain time-course from the beginning to end of the response
- It should be possible to derive the common parameters of comparison.
- It should be possible to derive the common parameters of comparison like 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.

ANNEX I: APPLICATION FORM FOR MARKETING AUTHORIZATION OF VETERINARY PHARMACEUTICAL PRODUCTS

General Instructions:

Provide as much detailed, accurate and final information as possible. Note that all areas are to be filled out by the applicant EXCEPT where indicated by grey areas which are for Official Use Only!

Should you have any questions regarding this form, please contact the EAC Reference Country.

A properly filled out and signed original copy of the form (including a soft copy in MS Word) must be submitted together with other application documents. The entire Common Technical Document should be submitted as per the requirements of NRAs.

APPLICATION FORM

FOR A MUTUAL RECOGNITION APPLICATION

FOR THE REGISTRATION OF VETERINARY PHARMACEUTICAL PRODUCT(S) IN THE EAST AFRICAN COMMUNITY

Draft agreed by Technical Working Group	16th Nov 2018
Draft released for consultation by representatives of East African region regulatory agencies	Dec 2018
End of consultation period	31st Dec 2018
Adoption by EAC	
EAC code	
Enters into force	

APPLICATION FORM FOR MUTUAL RECOGNITION REGISTRATION OF VETERINARY PHARMACEUTICAL PRODUCT(S) FOR THE EAST AFRICAN COMMUNITY

1.A Particulars of the Applicant

- Name:
- Physical address:
- Postal address:
- Phone: Fax: e-mail:

1.B Particulars of the Veterinary Pharmaceutical Product

- Product name:
- International Non-proprietary Name (INN) of the Active substance (active substance)
- Product strength
- Pharmaceutical form
- Anatomic Therapeutic Classification (ATC) Code
- Pack size(s):
- Types of packaging:
- Proposed shelf life (months)
- Proposed in-use shelf life where applicable
- Description of the Veterinary Pharmaceutical Product
- Main indication(s):
- Proposed distribution category

1.C **Name(s) and complete address(es) of the manufacturer(s) of the Finished Pharmaceutical Product including the final product release** if different from the manufacturer (Include the contract manufacturing and quality control laboratories)

	Name	**Manufacturing plant address including units and blocks**	**Activity**
1			
2			
3			
4			

Attach copies of certification of recognition of manufacturer from competent authority in the country of manufacture.

2. Authorised Local Technical *Representative (LTR) in Partner* States

Partner State	**Name of Local Technical Representative**	**Address of Local Technical Representative**
Burundi		
Kenya		
Rwanda		
United Republic of Tanzania		
Uganda		
South Sudan		

3. Current Registration and Licensing Status

3.1 Registration status in the country of manufacture (attach validated copy of marketing authorisation of Veterinary Pharmaceutical Product issued by the appropriate regulatory authority).

3.2 If not registered in the country of origin, provide Certificate of Origin issued by the competent authority in the country of manufacture.

3.3 If the Veterinary Pharmaceutical Product has been refused/deferred/cancelled/ withdrawn in any country or territory supply details

3.4 List of countries where the Veterinary Pharmaceutical Product is already registered.

4. Purpose of the application

4.1 A Mutual Recognition Procedure for a new product

- Reference Country:
- Procedure number: [*To be allocated by Co-ordination Group for MR*]
- Concerned Country(ies) (tick appropriate boxes below):

Partner State	
Burundi	
Kenya	
Rwanda	
United Republic of Tanzania	
Uganda	
South Sudan	

4.2. A Mutual Recognition Procedure for a product already licensed in one or more Partner States

- Reference Country:
- Date of authorisation: (dd-mm –yyyy):
- Licence number:

(a copy of the authorisation should be provided)

- Procedure number: [*To be allocated by Co-ordination Committee*]
- Concerned Country(ies) (tick appropriate boxes below):

Partner State	
Burundi	
Kenya	
Rwanda	
United Republic of Tanzania	
Uganda	
South Sudan	

Enclose a copy of the manufacturing license issued by the appropriate regulatory authority in the country of manufacture.

5. Product Composition

Give the composition of the product in terms of units per dose

5.1. Active (pharmaceutical) ingredients

Name	**Quantity per dose**	**Specification or reference text**

5.2. Inactive ingredients (excipients/preservative)

Name	**Quantity per dose**	**Specification or reference text**	**Reason for inclusion**

5.3. Additional Starting materials

Give details of any additional starting materials used in the manufacturing process but not found in the final product.

6. Type of Review Requested

Tick one of the options. Give reason(s) for the accelerated review request

Request	**Give reasons (if applicable)**
Normal Review	
Accelerated Review	

7. General Information and Supporting Documentation
For submission of the dossier, refer to guideline on dossier structure.

8. Declaration by applicant

I the undersigned hereby apply for registration of the product detailed above and declare that all the information herein and in the appendices is correct and true.

Fee enclosed:

Signed: Date:

Full name of Signatory:

ANNEX II TEMPLATE FOR THE PRODUCT INFORMATION

TEMPLATE FOR THE SUMMARY OF PRODUCT CHARACTERISTICS AND PACKAGING FOR VETERINARY PHARMACEUTICAL PRODUCTS

Draft agreed by Technical Working Group	15th Nov 2018
Draft released for consultation by representatives of East Africa region regulatory agencies	Dec 2018
End of consultation period	31st Dec 2018
EAC code	PSS/1/1/21/92
Enters into force	08 Feb 2019

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY PHARMACEUTICAL PRODUCT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance<s>:

<Excipient(s):>

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

The description of pharmaceutical form should include visual of the appearance of the product (colour, markings, etc.)

4. CLINICAL PARTICULARS

4.1 Target species

4.2 Indications for use, specifying the target species

4.3 Contraindications

4.4 Special warnings <for each target species>

4.5 Special precautions for use

i) Special precautions for use in animals

ii) Special precautions to be taken by the person administering the veterinary Pharmaceutical product to animals

4.6 Adverse reactions (frequency and seriousness)

4.7 Use during pregnancy, lactation or lay

4.8 Interaction with other Pharmaceutical products and other forms of

interaction

4.9 Amounts to be administered and administration route

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

4.11 Withdrawal period(s)

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

5. PHARMACOLOGICAL PROPERTIES

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

6.2 Incompatibilities

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

6.3 Shelf life

Shelf-life of the veterinary Pharmaceutical product as packaged for sale
Shelf-life after first opening the immediate packaging
Shelf-life after dilution or reconstitution according to directions where applicable
Shelf life after incorporation into meal or pelleted feed where applicable

6.4. Special precautions for storage

Do not store above <25 °C/30 °C
Store below <25 °C/30 °C
Store in a refrigerator (2 °C – 8 °C)
Store and transport refrigerated (2 °C – 8 °C)

Protect from light

6.5 Nature and composition of immediate packaging

<Not all pack sizes may be marketed.>

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

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

7. MARKETING AUTHORISATION HOLDER

{Name and address}
Tel:
Fax:
E-mail:

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10 DATE OF REVISION OF THE TEXT

{MM/YYYY} or <month YYYY>

CONTAINER LABELLING

Primary packaging and where applicable secondary packaging label

Every immediate and outer container of any Pharmaceutical product shall be labelled in legible and indelible letters. The labeling shall be in English and another language required by another Partner State or both.

1. NAME OF THE VETERINARY PHARMACEUTICAL PRODUCT

2. NAME AND QUANTITY OF ACTIVE SUBSTANCE(S)

3. TARGET SPECIES

4. INDICATION(S) with recommended dosage per target species

5. METHOD OF ADMINISTRATION and any warnings or precautions that may be necessary

6. CONTRAINDICATIONS
See package leaflet
For Animal Use Only

7. WITHDRAWAL PERIOD

8. BATCH NUMBER, MANUFACTURING DATE AND EXPIRY DATE INCLUDING IN-USE SHELF LIFE

9. PACK SIZE

10. STORAGE CONDITIONS and any handling precautions that may be necessary

11. THE NAME AND ADDRESS OF THE MANUFACTURER.

12. THE NAME AND ADDRESS OF THE COMPANY OR PERSON RESPONSIBLE FOR PLACING THE PODUCT ON THE MARKET IF DIFFERENT FROM THE MANUFACTURER

13. THE MARKETING AURTHORISATION NUMBER ONLY IF REQUIRED BY THE NATIONAL REGULATORY AUTHORITY (to be included after approval)

Blisters and strips

Blisters and strips should include, as a minimum, the following information printed direct on blister or/and strip:

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

PACKAGE LEAFLET

1. Name of the Veterinary Pharmaceutical product

2. Qualitative and quantitative composition

Active substance<s>:

<Excipient(s):>

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

3.1 Qualitative composition

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

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

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

3.2 Quantitative composition

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

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

Examples:
- Tablet – "White, circular flat bevelled-edge tablets marked '100' on one side".
- Solution for injection – "Pale yellow, clear solution for injection, pH 7.0"

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

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

Examples:
- "The tablets can be divided into equal halves".
- "The score line is intended to facilitate ease of swallowing and not to divide into equal doses".

4. Clinical particulars

4.1 Target species

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

4.2 Indications for use, specifying the target species

The indications should be clearly defined for the target species. It should be

clearly stated whether the treatment is for prophylactic, therapeutic or diagnostic purposes.

4.3 Contraindications

4.4 Special warnings for each target species

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

4.5 Special precautions for use

4.5.1 Special precautions for use in animals

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

4.5.2 Special precautions to be taken by the person administering the Pharmaceutical product to animals

Risks resulting from the nature of the product, its preparation and use and of any risks resulting from the particular characteristics of the user should be stated here.
Possible hypersensitivity reactions in the user to any of the excipients or residues from the manufacturing process should be included.

4.5.3 Other precautions

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

Examples:
The solvent in this product may stain certain materials including leather, fabrics, plastics and finished surfaces. Allow the application site to dry

before permitting contact with such materials.
This product is highly flammable. Keep away from heat, sparks, open flame or other sources of ignition.

Should not be allowed to enter surface waters as it has harmful effects on aquatic organisms.

4.6 Adverse reactions

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

4.7 Use during pregnancy, lactation or lay

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

4.8 Interaction with other Pharmaceutical products and other forms of interaction

4.9 Amount(s) to be administered and administration route

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

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

- "Signs as <description> may occur in <target specie> when the dose is exceeded.

"Do not exceed the recommended dose". (Effects which do not occur under normal treatment). And provide corrective measure if available

4.11 Withdrawal period(s)

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

<Not authorised for use in lactating animals producing milk for human consumption.>
<Do not use in pregnant animals which are intended to produce milk for human consumption within {X} months of expected parturition.>
<Not authorised for use in laying birds producing eggs for human consumption.>
<Do not use within {X} weeks of onset of the laying.>

5. Pharmacological properties

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

5.1 Pharmacodynamic properties

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

5.2 Pharmacokinetic particulars

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

5.3. Environmental properties

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

accumulation in the environment should be addressed.

6. Pharmaceutical particulars

6.1 List of excipients

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

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

6.2 Incompatibilities

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

In other cases, the standard term <None known> is used.
If incompatibility is not a concern due to pharmaceutical form of the product, e.g. solid oral pharmaceutical forms, the term used is <Not applicable>.

6.3 Shelf-life

<Shelf-life of the veterinary Pharmaceutical product as packaged for sale>
<Shelf-life after first opening the immediate packaging >
<Shelf-life after dilution or reconstitution according to directions >
<Shelf life after incorporation into meal or pelleted feed>

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

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

This section should include information necessary for the safe disposal of

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

7. Marketing Authorisation Holder

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

8. Date of revision of the text

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

ANNEX III: QUALITY OVERALL SUMMARY-(QOS)

General Instructions

Quality overall summary (QOS) template should be completed for pharmaceutical products containing active substances of synthetic or semi-synthetic 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 finished 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 EAC (EAC).

(a) Summary of product information:

Non-proprietary name of the finished pharmaceutical product (VPP)			
Proprietary name of the finished pharmaceutical product (VPP)			
International non-proprietary name(s) of the Active substance(s) (active substance(s)), including form (salt, hydrate, polymorph)			
Applicant name and address			
Applicant reference number (If already issued by EAC)			
Dosage form			
Reference Number(s)			
Strength(s)			
Route of administration			
Proposed indication(s)			
Withdrawal period			
Contact information	Name: Phone: Fax: Email:		

(b) Other Introductory information:

Related dossiers (e.g. VPP(s) with the same active substance(s) submitted to the EAC by the applicant):

Reference number (eg EAC/VM/0012)	**Registered (Y/N)**	**Active substance, strength, dosage form** (eg. oxytetracycline (as Hydrochloride) 20% w/v injectable solution	**Active substance manufacturer** (including address)

Identify available literature references for the active substance and VPP:

Publication(s)	Most recent edition/volume in which active substance/VPP appears	Most recent edition/volume consulted
ACTIVE SUBSTANCE status in pharmacopoeia and forum:		
Ph.Eur.		
BP		
USP		
Others		
VPP status in pharmacopoeia and forum:		
Ph.Eur.		
BP		
USP		
BP Veterinary codex		
Others		
Other reference texts (e.g. public access reports):		

STATUS OF GMP OF MANUFACTURING FACILITIES OF VPP (Official Use Only)
Compliance to GMP , marketing authorization and Certificate of pharmaceutical product (should be provided in Module 1) <insert inspection observations, comments, etc.>
ASSESSMENT OF LABELLING AND SAMPLES (Official Use Only)
Discussion/comments on the quality components of:
Prescribing information <insert assessment observations, comments, etc.>
Labelling (outer and inner labels) <insert assessment observations, comments, etc.>
Samples (e.g. VPP, device) <insert assessment observations, comments, etc.>

2.3.S Active Substance

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

Name of active substance:	
Name of active substance manufacturer:	
7	Certificate of suitability to the European Pharmacopoeia (CEP): • is a written commitment provided that the applicant will inform Reference Country in the event that the CEP is withdrawn and has acknowledged that withdrawal of the CEP will require additional consideration of the active substance data requirements to support the dossier: o 7 yes, 7 no; • A copy of the most current CEP (with annexes) and written commitment should be provided in Module 1. • The declaration of access should be filled out by the CEP holder on behalf of the VPP manufacturer or applicant. • Summaries of the relevant information should be provided under the appropriate sections (e.g. 3.2.S.1.3, 3.2.S.3.1, 3.2.S.4.1 through 3.2.S.4.4, S.6 and 3.2.S.7; see Quality guideline).
7	Drug master file (DMF) procedure: • DMF version number (and/or date) of the open part_____ ; version number (and/or date) of the closed part. • a copy of the letter of access should be provided in Module 1,as per the template in annex II of this guideline; and • Summaries of the relevant information from the Open part should be provided under the appropriate sections; see Section 3.2.S in the Quality guideline.
7	Full details in the PD: • Summaries of the full information should be provided under the appropriate sections; see Section 3.2.S in the Quality guideline.

2.3. S.1 General Information

2.3.S.1.1 Nomenclature

(a) International Non-proprietary name (INN):
(b) Compendial name, if relevant:
(c) Chemical name(s):
(d) Company or laboratory code:
(e) Other non-proprietary name(s) (e.g. national name, 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:
(c) Quantitative aqueous pH solubility profile

Medium (e.g.Physiological pH ranges in tagert animal(s)	**Solubility (mg/ml)**

(d) Physical form (e.g. polymorphic form(s), solvate, and hydrate):
Polymorphic form:
Solvate:
Hydrate:
(e) Other:

Property	
pH	
pK	
Partition coefficients	
Melting/boiling points	
Specific optical rotation (specify solvent)	
Refractive index (liquids)	
Hygroscopicity	
UV absorption maxima/molar 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, and storage) of each manufacturer, including contractors and each proposed production site or facility involved in these activities:

Name and address (including block(s)/unit(s))	**Responsibility**	**Active substance Master File/CEP number (if applicable)**

(b) Manufacturing authorization for the production of active substance(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):
(c) Alternate processes and explanation of their use:
(d) Reprocessing steps and justification:

2.3.S.2.3 Control of Starting Materials

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

Step/starting material	Test(s)/method(s)	Acceptance criteria

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

(c) Where the active substance(s) and the starting materials and reagents used to manufacture the active substance(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 of the active substance

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

Step/materials	Test(s)/method(s)	Acceptance criteria

2.3. S.2.5 Process Validation and/or Assessment

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

2.3. S.2.6 Manufacturing Process Development

Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the active substance used in producing comparative bioavailability or biowaiver, 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 active substance 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 active substance:
(e) Other characteristics:

2.3.S.2.3 Impurities

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

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

Active substance-related impurity (chemical name or descriptor)	**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**

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

(i) Maximum daily dose (i.e. the amount of active substance administered per day) for the active substance, corresponding to ICH Reporting/Identification/Qualification Thresholds for the active substance-related impurities and the concentration limits (ppm) for the process-related impurities (e.g. residual solvents):

Maximum daily dose for the active substance:	**<x mg/day>**	
Test	**Parameter**	**ICH threshold or concentration limit**
Active substance-related impurities	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, stability batches):

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

* include strength, if reporting impurity levels found in the VPP (e.g. for comparative studies)
** e.g. comparative bioavailability or biowaiver studies, stability

(iii) Justification of proposed acceptance criteria for impurities:

2.3. S.4 Control of the Active substance

2.3. S.4.1 Specification

(a) Active substance specifications of the VPP 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.		

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

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

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

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 biowaiver, stability)**

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

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

(c) Summary of analytical procedures and validation information for those 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 active substance specification (e.g. evolution of tests, analytical procedures and acceptance criteria, differences from officially recognized compendial standard(s)):

2.3. S.5.1 Reference Standards or Materials

(a) Source (including lot number) of primary reference standards or reference materials (e.g. Ph.Eur, BP, in-house):

(b) Characterization and assessment 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 active substance (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.g. 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, acid/base): and results:

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

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

Storage condition (1C, % RH)	**Batch number**	**Batch size**	**Container closure system**	**Completed (and proposed) testing intervals**

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

Test	**Results**
Description	
Moisture	
Impurities	
Assay	
etc.	

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

Container closure system	**Storage statement**	**Re-test period***

2.3. S.7.3 Stability Data

Refer to VICH GL3 guideline on stability requirement for testing new veterinary Drug substances

2.3. P VETERINARY PHARMACEUTICAL PRODUCT (VPP)

2.3. P.1 Description and Composition of the VPP

(a) Description of the VPP:

(b) Composition of the VPP**:**

(i) 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):

Component and quality standard (and grade, if applicable)	**Function**	**Strength (label claim)**					
		Quant. per unit	**%**	**Quant. per unit**	**%**	**Quantity per unit**	**%**
<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							

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

- Description of accompanying reconstitution diluent(s), if applicable:
- Type of container closure system used for the VPP 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 substance

(a) Discussion of the:

(i) Compatibility of the active substance(s) with excipients listed in 2.3.P.1:

(ii) Key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the active substance(s) that can influence the performance of the VPP:

(iii) For fixed-dose combinations, compatibility of active substances 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 VPP performance):

2.3. P.2.2 Veterinary pharmaceutical 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 process parameters and formulation, etc.):

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

(i) Summary of batch numbers:

Batch number(s) of the VPPs used in			
Bioequivalence or biowaiver			
Dissolution profile studies			
Stability studies (primary batches)			
‹			
Stability studies (production batches)			
Validation studies (primary batches) if available			
Validation studies (at least the first three consecutive production batches) or code(s)/version(s) for process validation protocol(s)			

(ii) Summary of formulations and discussion of any differences:

Component and quality standard (e.g. BP, Ph.Eur, in-house)	**Relevant Batches**					
	Stability		**Process validation**		**Commercial (2.3.P.1)**	
	<Batch nos. and sizes>		**<Batch nos. and sizes>**		**<Batch nos. and sizes>**	
	Theor. quantity per batch	**%**	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**
Subtotal 1						
Subtotal 2						

Component and quality standard (e.g. BP, Ph.Eur, in-house)	**Relevant Batches**					
	Stability		**Process validation**		**Commercial (2.3.P.1)**	
	<Batch nos. and sizes>		**<Batch nos. and sizes>**		**<Batch nos. and sizes>**	
	Theor. quantity per batch	**%**	**Theor. quantity per batch**	**%**	**Theor. quantity per batch**	**%**
Total						

(c) 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):

(d) Summary of results for comparative in vitro studies (e.g. dissolution):

(e) Summary of any information on in vitro-in vivo correlation (IVIVC) studies (with cross-reference to the studies in Module 5):

(f) For scored tablets, provide the rationale/justification for scoring:

2.3. P.2.2.2 Overages

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

2.3.P.2.2.3 Physicochemical and Biological Properties

Discussion of the parameters relevant to the performance of the VPP (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 VPP (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

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

2.3. P.2.6 Compatibility

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)

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

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

2.3.P.3.2 Batch Formula

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.g. number of dosage units)			
Component and quality standard	**Quantity per dosage unit (e.g. mg/ml**	**Quantity per batch (e.g. kg/batch)**	**Function of ingredients**
<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:
(b) Narrative description of the manufacturing process, including equipment type and working capacity, process parameters:
(c) Justification of reprocessing of materials where applicable:

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:

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. These can be among others: steps where
significant impurities are removed or introduced, steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation, 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.

Step (e.g. granulation, compression, coating, sterilization)	**Controls**

2.3.P.3.5 Process Validation and/or Assessment

It is expected that the manufacturing processes for all APIs are properly controlled. If the API is prepared as sterile, a complete description should be provided for aseptic processing and/or sterilization methods. The controls used to maintain the sterility of the API during storage and transportation should also be provided. Alternate processes should be justified and described.

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

Summary of the process validation and/or assessment 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, and results):

2.3. P.4 Control of Excipients

2.3.P.4.1 Specifications

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

2.3.P.4.2 Analytical Procedures

Summary of the analytical procedures for supplementary tests:

2.3.P.4.3 Validation of Analytical Procedures

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

2.3.P.4.4 Justification of Specifications

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 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:

(b) CEP(s) demonstrating TSE-compliance can be found in:

2.3.P.4.6 Batch analysis of the excipients

Summary of batch analyses for each excipient

2.3.P.5 Novel Excipients

For excipients not described in a pharmacopoeia, the specification and routine tests should be summarised. Where the excipient is used for the first time in pharmaceutical product full data must be provided in the quality guideline module 3 on nomenclature, description, manufacture, quality control during manufacture etc. (as for an Active Substance),

2.3.P.6 Control of VPP

2.3.P.6.1 Specification(s)

Specification(s) for the VPP:

Standard (e.g. BP, Ph Eur, In 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.6.2 Analytical Procedures

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

See annex I of module 3 for summaries of the analytical procedures and validation information

2.3. P.6.3 Validations of Analytical Procedures

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

2.3. P.6.4 Batch Analyses

(a) Description of the batches:

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

(b) 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.				

(c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.6.2 and 2.3.P.6.3 (e.g. historical analytical procedures):

2.3. P.6.5 Characterisation of Impurities

(a) Identification of potential and actual impurities:

Degradation product (chemical name or descriptor)	**Structure**	**Origin**

Process-related impurity (compound name)	**Step used in the VPP manufacturing process**

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

(i) Maximum daily dose (i.e. The amount of active substance administered per day) for the active substance, 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):

Maximum daily dose for the active substance:	**<x mg/day>**	
Test	**Parameter**	**VICH threshold or concentration limit**
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):

Impurity (degradation product and process-related)	**Acceptance criteria**	**Results**		
		<batch no., strength, use>		

(iii) Justification of proposed acceptance criteria for impurities:

2.3. P.6.6 Justification of Specification(s)

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

2.3. P.7 Reference Standards or Materials

(a) Source (including lot number) of primary reference standards or reference materials (e.g. BP, in-house) not discussed in 3.S.1.5

(b) Characterization and assessment 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.S.1.5:

(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.S.1.5:

2.3. P.8 Container Closure System

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

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

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

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

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

2.3. P.9 Stability

2.3. P.9.1 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):

Storage conditions (1C, % RH)	**Strength and batch number**	**Batch size**	**Container closure system**	**Completed (and proposed) test intervals**

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

Test	**Results**
Description	
Moisture	
Impurities	
Assay	
etc.	

(e) Summary of in use stability studies

Storage conditions (1C, % RH)	batch number	Batch size	Container closure system	Completed (and proposed) test intervals

Summary of in use stability results observed for the above stability studies:

Test	Results
Description	
Moisture	
Impurities	
Assay	
etc.	

(d) 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.9.2 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 ongoing stability batches, if applicable

ANNEX IV: PRODUCT QUALITY REVIEW REQUIREMENTS FOR ESTABLISHED MULTISOURCE PRODUCTS

For an established generic product a product quality review may satisfy the requirements of Sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and QOS-PD.
A product quality review should be submitted with the objective of verifying the consistency of the quality of the VPP and its manufacturing process.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.
Reviews should be conducted with not less than 10 consecutive batches manufactured over the period of the last 12 months, or, where 10 batches were not manufactured in the last 12 months, not less than 25 consecutive batches manufactured over the period of the last 36 months and should include at least:

1. A review of starting and primary packaging materials used in the VPP, especially those from new sources.

2. A tabulated review and statistical analysis of quality control and in-process control results.

3. A review of all batches that failed to meet established specification(s).

4. A review of all critical deviations or non-conformances and related investigations.

5. A review of all changes carried out to the processes or analytical methods.

6. A review of the results of the stability-monitoring programme.

7. A review of all quality-related returns, complaints and recalls, including export- only pharmaceutical products.

8. A review of the adequacy of previous corrective actions.

9. A list of validated analytical and manufacturing procedures and their revalidation dates.

Notes
Reviews must include data from all batches manufactured during the review period.

Data should be presented in tabular or graphical form (i.e. charts or graphs), when applicable.

Annex V: Letter of Access to EAC-APIMF

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

<Applicant's reference> <Date>
<National Medicines Regulatory Authority>
<Address>
<Address>
<Post code><Town>
<Country>

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 (*Name EAC-NMRA*) to refer 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 (*name of EAC-NMRA*) 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)

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 EAC Active Pharmaceutical Ingredient Master File Procedure has been supplied to the applicant (**where applicable**).

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 EAC-NMRA 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 EAC 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 EAC before written approval is granted by the NMRA.

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 [*name(s) of EAC NMR(s)*] is authorized to request and refer to the evaluation reports of these agencies. The (*EAC-NMRA*) is also authorized to exchange its own evaluation reports with these and other regulatory authorities (where applicable).

Any questions arising from the EAC-NMRA's evaluation of this APIMF should be forwarded to:

{Name and address}

Yours faithfully

{Signature of Company Representative}
{Name}
{Position in Company}
{Date}

ANNEX VI: Authorization to access Certificate of Suitability (CEP)

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

<Applicant's reference> <Date>

<National Medicines Regulatory Authority>
<Address>
<Address>
<Post code><Town>
<Country>

Dear Sir/Madam,

Subject: Authorization to access Certificate of Suitability (CEP)

Reference is made to the above subject matter.

Consent is hereby granted to (*Name EAC-NMRA*) to refer 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 (*name of EAC-NMRA*) 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:
(*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 and to EAC-NMRA 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 EAC 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 EAC before written approval is granted by the NMRA.

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 EAC-NMRA's evaluation of this CEP should be forwarded to:
(*Name and address*)

Yours faithfully

{Signature of Company Representative}
{Name}
{Position in Company}
{Date}