GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR RENEWAL OF MARKETING AUTHORIZATION OF VETERINARY PHARMACEUTICAL PRODUCTS

Document Number:	Effective Date:	Review Date
Revision Number:	Revision Date:	

TABLE OF CONTENTS

ABBREVIATIONS

API	-	Active Pharmaceutical Ingredient
CEP	-	Certificate of Suitability to the European Pharmacopeia
DMF	-	Drug Master File
FPP	-	Finished Pharmaceutical Product
GMP	-	Good Manufacturing Practices
VICH	-	International Cooperation for Harmonization of Technical Requirements for Veterinary Medicinal Products
INN	-	International Non-proprietary Name
OoS	-	Out of Specification
PD	-	Product Dossier
PIL	-	Product Information Leaflet
POM	-	Prescription Only Medicine
SmPC	-	Summary of Product Characteristics
VMD	-	Veterinary Medicines Directorate

1 INTRODUCTION

Section 19. (1) of the Veterinary Medicines Regulations LN. No. 209 of 2015 prescribes that a person shall not import, manufacture, sell, transport or distribute any veterinary medicine in Kenya unless that veterinary medicine has been registered.

It is acknowledged that in the course of five (5) years, several aspects of a registered medicinal product may change significantly as a result of notified variations and other unnotified changes in manufacturing and control of the products. These may have a significant impact on the respective product and, therefore, the objective of renewal of registration is to ensure that the product continues to conform to the above-mentioned requirements.

Section 23. (4) further prescribes that a certificate of registration issued under these Regulations shall, unless suspended or revoked, be in force for a period of five years
Furthermore, section 24. (1) says that a person may make an application to the Council for renewal of registration of a veterinary medicine.

Section 24. (2-3) and 25 (1-5) provide for requirements for the application for renewal of registration of a medicinal product.

The guidelines therefore accommodate the steps that are followed from the submission of a dossier to the final outcome, the timeframe and procedure for the Directorate to evaluate renewal of registration of a particular product.

The guidelines are divided into three major parts stipulating the general requirements and application procedures for veterinary medicinal products; processing of applications; and technical requirements for application for renewal of medicinal products.

Applicants are requested to carefully read these guidelines, fill in the application forms, and upload the relevant sections of the dossier in the VMD online application portal.

The guidelines present current thinking on technical requirements necessary to facilitate renewal of registration of medicinal products. It is worth noting that the Directorate will evaluate products based on up-to-date scientific knowledge and standards known or existing at the time of evaluation. Applicants are therefore encouraged to keep abreast of scientific developments and apply the most current scientific information and technology to develop and test their products.

Applicants are also requested to read these guidelines together with the other relevant legislation.

2 GLOSSARY

In the context of these guidelines, the following words/phrases are defined as follows: -

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

Directorate
Means the Veterinary Medicines Directorate, or its acronym – VMD.

Drug Master File
A drug master file (DMF) is a master file that provides a full set of data on an API.

Finished Pharmaceutical Product (FPP)
Means a product that has undergone all stages of production, including packaging in its final container and labelling.

Manufacturer
Means a person or firm that is engaged in the manufacture of pharmaceutical products.

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.

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

Registration for a medicine or Marketing Authorization
Means registration of a veterinary medicine by the Council and the issuance of a registration certificate under VMD regulations.

Variation
Means a change to any aspect of a medicinal product post registration, 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.

3 SCOPE

These guidelines are relevant for the application for renewal of marketing authorization of veterinary medicinal products registered in Kenya.

4 POST RENEWAL VARIATION TO VETERINARY MEDICINAL PRODUCTS

All variations to a registered pharmaceutical product shall be made according to the requirements stipulated in the *Application Guidelines for Variation of Registered Veterinary Medicinal Products*. No variation will be accepted during the submission of the renewal of registration.

5 REQUIREMENTS FOR RENEWAL APPLICATIONS

5.1 GENERAL REQUIREMENTS AND APPLICATION PROCEDURES

Applications should be made to the Directorate at least ninety (90) days before the expiry of the validity of registration of a particular medicinal product. Please make note of the following:

1.1.1 All applications and supporting documents shall be in English. The submitted documents, which are in any language other than English, must be accompanied by a certified or notarized English translation.

1.1.2 The responsibility of applying for renewal of product registration remains with the company responsible for the introduction of the product into the Kenyan market, i.e., the Marketing Authorization Holder (MAH).

1.1.3 Applications must be duly completed and supported by all the required documents as stipulated in these guidelines and, where appropriate, in line with the current edition of the *guidelines for registration of veterinary pharmaceutical products.*

1.1.4 The application should be submitted online along with a non-refundable product **applicable fee** The evidence of payment of the fees must be presented at the time of submission of the product samples.

1.1.5 Two samples of the smallest commercial pack(s) from a single batch, along with their **certificates of analysis,** should be submitted. Kindly note that a complete application includes the submission of physical samples. Therefore, the date of submission of the samples will be considered as the date of receiving the renewal application.

1.1.6 The evidence of conformance of the finished product manufacturing facility with the current good manufacturing practice (GMP) requirements as prescribed in the GMP guidelines should be provided.

1.1.7 A list of all countries should be provided, where the product has been reviewed and approved over the registration period of the product, along with their registration numbers. If available, copies of registration certificates should be submitted.

5.2 PROCESSING OF APPLICATIONS (MANAGEMENT OF APPLICATIONS)

The following stages are involved for renewal applications from the time of application submission to the final outcome:

1.1.8 Upon receipt of an application, a tracking number will be auto-generated.

1.1.9 Pre-checking will be done by the Directorate, and if satisfactory the application will be moved to the next assessment step. if unsatisfactory there will be a communication by the Directorate to the applicant regarding the application status.

1.1.10 Evaluation of the application shall be carried out within six (6) months from the date of submission, and the respective outcomes will be communicated to the applicant(s).

1.1.11 During evaluation, the Directorate may request further information and additional supporting documents from the applicant. Required information should be made available within sixty (60) days from the date of the request so as to facilitate the timely renewal of the applied product.

1.1.12 Notification for renewal of registration of the product shall be communicated, followed by the issuance of a new registration certificate.

5.3 TECHNICAL REQUIREMENTS FOR APPLICATION FOR RENEWAL OF MEDICINAL PRODUCTS

Applications must be duly completed and supported by all the required documents, as stipulated in this guideline and supplementary documents. The following submissions are required:

(b) Cover letter
(c) Product information in CTD format as outlined in 5.3.1, 5.3.2 and 5.3.3.
(d) Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.
(e) List of all variations approved during the validity of registration.
(f) Quality Information Summary (QIS) in MS Word Format
(g) Product Quality Review
(h) Vigilance and Product Safety Reports (Including Risk Management Plan) as outlined in 5.3.4.
(i) Two samples of the finished product packaged for sale.
(j) Mock-up artworks

5.3.1 ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)]

1.1.12.1 Names and complete addresses of all current suppliers of active pharmaceutical ingredient(s) along with manufacturing and GMP certificates of the active pharmaceutical ingredient(s) manufacturing facilities issued by competent regulatory authorities.

1.1.12.2 Copy of current signed, dated and numbered specifications and analytical

procedures used for testing the active pharmaceutical ingredient(s) by the finished product manufacturer.

1.1.12.3 Information on container-closure system used for storage of the API in FPP manufacturer's storage facilities, storage conditions specified for the API and re-test period/shelf life implemented for the respective API;

5.3.2 FINISHED PHARMACEUTICAL PRODUCT (FPP)

1.1.12.4 Detailed description of qualitative and quantitative composition of the unit dosage form and of the commercial batch size(s) approved including colourants, coating agents in a manner provided for in section 3.2.P.1 of the main registration guidelines.

1.1.12.5 A copy of batch manufacturing record (BMR) for the largest production batch manufactured within six months before the date of submission of the renewal application.

1.1.12.6 Report on annual product quality review for all batches of the finished product manufactured in the past 36 months before the date of application of the renewal. At minimum the report should include the following:

a) A review of starting and primary packaging materials used in the FPP, especially those from new sources.
b) A tabulated review of quality control and in-process control results.
c) A review of all batches that failed to meet established specifications.
d) A review of all changes carried out to the processes or analytical methods.
e) A review of the results of the stability monitoring programme; and
f) A list of validated analytical and manufacturing procedures and their revalidation dates.

1.1.12.7 A copy of current signed, dated and version numbered release and shelf-life specifications of the finished products along with standard testing procedures.

1.1.12.8 Information on container closure system(s). Data should be submitted according to the requirements stipulated under section 3.2.P.7 of the main registration guidelines for veterinary medicinal products.

1.1.12.9 Data on stability study. For pharmaceutical products previously registered with long term stability data which do not support stability of the product under zone IVB conditions, data should be provided to demonstrate stability of the product under storage conditions of 30^{O}C ± 2^{O}C/75% ± 5% relative humidity. Studies should be conducted according to requirements stipulated under section 3.2.P.8 of the main Guidelines on Submission of Documentation for Registration of Veterinary Medicinal Products and specific guidelines on Stability Testing Requirements for Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs).

1.1.12.10 List of all variations (any minor and/or major changes) submitted to and accepted by the Directorate over the registration period of the product.

Reference number	Description of the change	Date submitted	Approval/Rejection date and reference number of the letter	Implementation status

5.3.3 PRODUCT INFORMATION

1.1.12.11 Specimen of the current package insert and copies of colored mock-up labels of the product.

1.1.12.12 All prescription medicines should be accompanied by the SmPC presented in both PDF and Microsoft Word formats.

1.1.12.13 All pharmaceutical preparations with potential for long-term use and general sales medicines must contain a Product Information Leaflet (PIL). Languages used for PIL and labelling should be clearly expressed in English.

1.1.12.14 Submission of periodic post-marketing surveillance and safety studies for evaluation and determination of risk risk-benefit profile of the registered product. The periodic safety update reports (PSURs) should include information on the adverse effects observed for the product on the market.

5.3.4 PERIODIC SAFETY UPDATE REPORTS (PSURs)

PSURs are pharmacovigilance documents intended to provide an evaluation of the risk-benefit balance of a medicinal product at defined time points after its authorization.

The objective of the PSUR is to present a comprehensive and critical analysis of the risk-benefit balance of the product, taking into account new or emerging safety information in the context of cumulative information on risk and benefits.

The PSURs should be prepared according to the guidelines on good pharmacovigilance practice.

2. Environmental Risk Assessment (ERA)

Applicants must confirm that the original ERA remains valid.

Updated ERA data is required where triggers apply e.g.,

a) Increased usage or market expansion
b) New data on environmental safety concerns
c) New evidence of antimicrobial resistance

The requirements must follow VICH GL6 and related ERA guidelines

ANNEX 1: APPLICATION FORM FOR RENEWAL OF REGISTRATION OF VETERINARY PHARMACEUTICAL PRODUCTS

General Instructions:

Please read all the instructions carefully prior to completing this Application form.

Provide as much details, accurate and complete information as possible. Note that all areas are to be filled out by the applicant EXCEPT where indicated by GREY COLOURS, which are for Official Use Only.

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

Before submitting the completed form, please double-check to confirm whether you have provided all the requested information.

This application form should be accompanied by a Batch Manufacturing Record (BMR) of all commercial batches manufactured within the last six months from the date of submission of this application.

Should you have any questions regarding this form, please contact the Directorate.

A properly filled out and signed original copy of the form with all its annexes must be submitted together with the veterinary medicinal product quality part of the dossier electronically.

For official use only

1.1 Application Number		
1.2 Date of submission of the dossier		
1.3 Evaluator	Name	Signature
1.4 Auditor	Name	Signature
1.5 Date of evaluation		
1.6 Date of auditing		
1.7 Number of files		
Conclusion of the assessment *If the dossier is* **RECOMMENDED,** *specify:* • *Primary packaging and shelf-life of product,* • *Storage conditions of the product and special precautions.* • *Distribution category*	**RECOMMENDED (no outstanding issues)** **QUERY RAISED** **REJECTED** **(*Please delete which does not apply*)**	
2. To be filled in by the applicant		
Category of the medicinal product		

2.1 Registration number	

2.2Date of expiry of current registration	
2.3Proprietary Name of the Product	
2.4International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength,	
2.5 Dosage Form	
2.6 Route of administration	
2.7 Anatomic Therapeutic Classification (ATC) Code	
2.8 Name and address (physical and postal) of Applicant	
2.9 Name and address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s). *(Add as many rows as necessary)*	
2.10 Site/location of manufacture of API (s)	
2.11 Name(s) and complete address (es) of the manufacturer(s) of the finished product(s), including the final product release if different from the manufacturer. *(Add as many rows as necessary)*	
2.12. Site/location of manufacture of FPP	
2.13 Name and complete address of the Local Technical Representative (LTR)	
2.14 Visual physical description of the FPP	
2.15 Packing/pack size	
2.16 Proposed shelf life (in months)	

2.17 Proposed shelf life (after reconstitution or dilution)	
2.18 Proposed shelf life (after first opening container)	

2.19 Proposed storage conditions	
2.20 Proposed storage conditions after first opening	
2.21 Distribution category: e.g., Controlled Drug ☐ POM ☐ General sale ☐ (Applicants are invited to indicate which categories they are requesting; however, the VMD reserves the right to change and/or apply only those categories provided for in their national legislation)	
2.22 Country of origin	
2.23 Current registration status in other countries	

1 FINISHED PHARMACEUTICAL PRODUCT(s) [FPP(s)]	
1.1 Manufacturing and Marketing authorization	
1.2 Formulation	
Strength (label claim)	
Master Production Document Reference Number and/or Version	
Batch Size (number of dosage units)	

Ingredients (APIs and excipients) starting with APIs	Quality standard	Specification	Dosage per unit composition		Batch quantities	
			mg	%	kg	%
Film coating						

Composition of all *components that are mixtures* (e.g., colorants, coatings, imprinting inks):

Description of accompanying reconstitution diluents (s), if applicable:

1.3 Control of the FPP

1.3.1 Specifications for the FPP

Standard Claimed (e.g., In-house, BP, Ph. Eur., Ph. Int., USP)			
Specification Reference Number and/or Version			
Test	Analytical Procedure (Type/Source/Version)	Acceptance Criteria	
		Batch release	Shelf life

1.4 Container/closure system(s) and other packaging

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

(b) Materials of construction of each primary packaging component:

(c) Summary of specifications of each primary and functional secondary packaging components:

1.5 Completed real-time stability testing:

Applicable only if registration was based on accelerated and partial real-time stability data

Stability protocol for continuing (i.e., ongoing) batches:

Protocol Parameter	Description
Storage conditions (including tolerances)	
Testing frequency	
Number of batches per strength and batch sizes	
Container closure system(s)	
Stability-indicating quality parameters	
Photostability testing	
Tests and acceptance criteria	
Other	

FPPs packaged in impermeable containers
FPPs packaged in semi-permeable containers
Evaluation
(a) Summary of stress testing and results (e.g., photostability studies, cyclic studies for semi-solids, freeze-thaw studies):

(b) Summary of real-time testing (e.g., studies conducted, protocols used, results obtained):

(i) Description of stability study details:

Storage Conditions (°C, %RH)	Batch Number	BatchSize	Container Closure System	Completed (and Proposed) Test Intervals (in months)

(ii) Summary and discussion of stability study results:

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

Extrapolation of data

Core storage statements
1.6 3Container labelling
1.6.1 Packaging or, where there is no outer packaging, on the immediate packaging

1.6.2 Blisters and strips
1.7 Current Product Information Leaflet
2 PERIODIC SAFETY UPDATE REPORTS (Attach)

3 DECLARATION BY AN APPLICANT

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

I further confirm that the information referred to in my application dossier is available for verification during GMP inspection.

I also agree that I shall carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports to the Directorate.

I also consent to the consideration of information provided by the users.

It is hereby confirmed that fees will be paid/have been paid according to the Veterinary Medicines Directorate, Kenya

Name:
……..…….

Position in the company

……

Signature:…….……

Date:…….

Official stamp:……..

ANNEX 2: QUALITY INFORMATION SUMMARY (QIS)

a. Summary of product information:

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

b. Administrative Summary:

Applicant's date of preparation or revision of the QIS	
Version and/or date of acceptance	*(official use only)*

Related dossiers (e.g. FPP(s) with the same API(s) submitted to VMD by the applicant):

Application number ( )	Registration status (Y/N)	API, strength, dosage form (e.g., Irinotecan (as chloride) 20mg per ml Solution)	API manufacturer (including address if the same manufacturer as the current dossier)

DRUG SUBSTANCE (or ACTIVE PHARMACEUTICAL INGREDIENT (API)) (NAME, MANUFACTURER)

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

Name of API:	
Name of API manufacturer:	
□	Certificate of suitability to the European Pharmacopoeia (CEP) Option 1.
□	Confirmation of API prequalification document: Option 2
□	API approval number _____ . Option 3a.
□	Active pharmaceutical ingredient master file (APIMF) procedure: APIMF number assigned by VMD (if known):_____; version number(s) including amendments (and/or date(s)) of the open part:_____; version number(s) including amendments (and/or date(s)) of the restricted part: _____. Option 3b.
□	Full details in the Product Dossier (PD) Open part DMF version number,_____ Restricted part DMF version number_____ Identifier of current module 3.2.S: _____ Option 4.

3.1 Manufacture (name, manufacturer)

3.1.1 Manufacturer(s) (name, manufacturer)

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

Name and address (including block(s)/unit(s))	Responsibility	CEP number/ WHOAPI-PQ number /WHO APIMF/ VMD registration No./Approved APIMF/ if applicable)	Letter of access provided?

3.1.2 Control of Materials (name, manufacturer) – <u>for API option 4 only</u>

(a) **Name of starting material:**

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

3.1.3 Control of the API (name, manufacturer)

3.1.4 Specification (name, manufacturer)

(a) **API specifications *of the FPP manufacturer:***

Standard (e.g., Ph. Int., Ph. Eur., BP, USP, in-house)		
Specification reference number & version effective date		
Test	**Acceptance criteria**	**Analytical procedure (Type/Source/Version)**
Description		
Identification		
Impurities		
Assay		
etc.		

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

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

2.3.S.7 Stability (name, manufacturer)

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

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

Container closure system	Storage statement	Re-test period*

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

1 DRUG PRODUCT (or FINISHED PHARMACEUTICAL PRODUCT (FPP))

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

Name of API:	
Name of API manufacturer:	
•	Full details
•	WHO collaborative procedure
•	SRA Abridged procedure
•	EAC Mutual Recognition
•	EU Article 58 procedure

1.1 Description and Composition of the FPP

(a) Description of the FPP (in signed specifications):

(b) Composition of the FPP:

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

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

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

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

1.1.1 Formulation Development

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

(i) Summary of batch numbers:

Batch number(s) of the FPPs used in

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

Summary of formulations and discussion of any differences:

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

Subtotal 1								
<complete with appropriate title e.g. Film-coating>								

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

1.2 Manufacture

1.2.1 Manufacturer(s)

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

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

1.2.2 Batch Formula

Largest intended commercial batch size:

Other intended commercial batch sizes:

< Information on all intended commercial batch sizes should be in the QIS>

(b) List of all components of the FPP to be used in the manufacturing process and their amounts on a per batch basis (including 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 (and grade, if applicable)	**Quantity per batch (e.g. kg/batch)**	**Quantity per batch (e.g. kg/batch)**	**Quantity per batch (e.g. kg/batch)**
<complete with appropriate titles, e.g. Core tablet (Layer 1, Layer 2, etc., as applicable), Contents of capsule, Powder for injection>			
Subtotal 1			
<complete with appropriate title, e.g. Film-coating >			
Subtotal 2			
Total			

1.2.3 Description of Manufacturing Process and Process Controls

(c) Flow diagram of the manufacturing process:

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

1.2.4 Controls of Critical Steps and Intermediates

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

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

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

1.2.5 Process Validation and/or Evaluation

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

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

1.3 Control of FPP

1.3.1 Specification(s)

(a) Specification(s) for the FPP:

Standard (e.g., Ph. Int., BP, USP, 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.			

1.3.2 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)	**Strength**	**Unit count or fill size (e.g. 60s, 100s etc.)**	**Container size (e.g. 5 ml, 100 ml, etc.)**

1.3.3 Stability

1.3.3.1 Stability Summary and Conclusions

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

Container closure system	Storage statement	Shelf-life

1.3.3.2 Post-approval Stability Protocol and Stability Commitment

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

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

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

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

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

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

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

2.3.P.7.2 Stability Data

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

WRITTEN COMMITMENTS OF THE MANUFACTURER – for official use

If applicable (primary stability study commitment):

The Applicant (or API manufacturer) undertook in writing (date of letter of commitment) to continue long- term testing of <INN of API> for a period of time sufficient to cover the whole provisional re-test period (period ending month/year) and to report any significant changes or out-of-specification results immediately to VMD for the specific batches: (Batch numbers, manufacturing dates, batch size, primary packing materials)

If applicable (commitment stability studies):

Since stability data on three production scale batches were not provided with the application, the remaining number of production scale batches should be put on long-term stability testing. Any significant changes or out-of-specification results should be reported immediately to VMD. The approved stability protocol should be used for commitment batches.

API option 1 – CEP

The Applicant provided a commitment in writing (date of letter of commitment) to inform VMD in the event that the CEP is revised or withdrawn, and that revisions to the CEP will be handled as per variation guidelines. Note that revisions or withdrawal will require additional consideration of the API data requirements to support the dossier.

API option 2 – WHOAPI-CPQ

The Applicant provided a commitment in writing (date of letter of commitment) to inform VMD in the event that the WHOAPI-CPQ is revised or withdrawn, and that revisions to the WHOAPI-CPQ will be handled as per VMD Variation guidelines. Note that revisions or withdrawal will require additional consideration of the API data requirements to support the dossier.

API option 3 – full details in the Product Dossier (ongoing stability study commitment)

The Applicant undertook in writing (date of letter of commitment) a commitment regarding ongoing stability studies. Unless otherwise justified, at least one batch per year of the product will be included in the stability programme (unless none is produced during that year). The stability protocol will be

that which was approved for primary batches (or the protocol was submitted for assessment). Out-of-specification results or significant atypical trends will be investigated. Any confirmed significant change or out-of-specification result will be reported immediately to VMD. The possible impact

on batches on the market will be considered in consultation with the GMP inspection.

FPP

If applicable (primary stability study commitment):

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

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

If applicable (commitment stability studies):

Since stability data on three production scale batches was not provided with the application, the Applicant undertook in writing, (date of letter of commitment) to put the remaining number <e.g. additional two (2)> production scale batches of < FPP reference number, trade name (INN of API), strength, pharmaceutical form, primary packing material> on long-term stability testing. Any out-of-specification results or significant changes during the study will immediately be reported to VMD. The approved stability protocol will be used for commitment batches.

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

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

Ongoing stability study commitment

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

If applicable (validation of production batches)

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