LIBERIA MEDICINES & HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

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GUIDELINES FOR

REGISTRATION OF MEDICINES & HEALTH PRODUCTS IN LIBERIA

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Much recognition is given to the Guideline Drafting Team which includes Pharm. Patricia Quaye-Freeman, Director of Evaluation of Registration; Pharm. Mary G. Jalloh-Tozo, Deputy Director of Evaluation of Registration; Pharm. Emmanuel Willie, Data & Research Manager; Pharm. Alexander Momo; Dr. Sumo Maiwo; and Pharm. Humphrey Taylor. Our heartfelt thanks also go to Dr. Flomoku G. Miller, Technical Advisor to the Managing Director, for his encouragement, technical and moral support to the Guideline Drafting Team.

We also acknowledge and give recognition to the World Health Organization (WHO) and the International Committee on Harmonization (ICH) for making available documents which were used as resource materials in the compilation of this guideline.

Most importantly and above all else, we sincerely give thanks and praises to the Almighty God for endowing us with the insight, resourcefulness and strength to draft this guideline. The guideline, along with other quality documents, shall constitute the legal basis for the evaluation and registration of medicines and health products in Liberia.

The LMHRA Evaluation and Registration Department shall welcome comments/suggestions for improvement of this guideline during its implementation.

STATEMENT FROM THE MANAGING DIRECTOR

As a National Regulatory Agency for medicines and health products, the Liberia Medicines and Health Products Regulatory Authority is responsible to ensure the efficacy, quality and safety of all medicines and health products that circulate on the Liberian market. Additionally, it is incumbent upon the Authority to adequately disseminate relevant information for public consumption, and create a working tool for utilization by the public.

Against this background, these guidelines have been developed to provide guidance for all Pharmaceutical entities in Liberia.

I appreciate the contribution of the Quality Control Laboratory and the team of validators for their guidance in the development of the Registration Guidelines.

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MANAGING DIRECTOR
LIBERIA MEDICINES AND HEALTH PRODUCTS REGULATORY AUTHORITY (LMHRA)

LIST OF ABBREVIATIONS

API	Active pharmaceutical ingredient
APIMF	Active pharmaceutical ingredient master file
BCS	Biopharmaceutics Classification System
BP	British Pharmacopoeia
CEPT	Certificate of Suitability
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
DMF	Drug Master File
DOS-PD	Dossier Overall Summary of Product Dossier
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
ICH	International Council for Harmonization
IVIVC	in vitro-in vivo correlation
JP	Japanese Pharmacopoeia
LMHRA	Liberia Medicines & Health Products Regulatory Authority
OTC	Over-the-counter
Ph.Eur.	European Pharmacopoeia
Ph.Int.	The International Pharmacopoeia
QIS	Quality Information Summary
QOS	Quality Overall Summary
SmPC	Summary of Product Characteristics
SOP	Standard operating procedure
USP	United States Pharmacopeia
WHO	World Health Organization

GLOSSARY

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

Active pharmaceutical ingredient (API)

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

Allopathic

A product or substance other than a medical device, which is to be administered to one or more human beings on its own, or as an ingredient in the preparation of a substance, for a medicinal purpose.

API starting material

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

Applicant

The person or entity who submits an application for product registration to the Authority is responsible for all the product information.

Authorized local agent (Representative)

Any pharmaceutical company or Pharmacist established within a country or jurisdiction who has received a mandate from the manufacturer to act on his behalf for specified tasks with regard to the manufacturer's obligations under legislation of the medicine and other regulatory guidance's issued by the Authority.

Batch records

All documents associated with the manufacture of a batch of bulk product or finished product. They provide a history of each batch of product and of all circumstances pertinent to the quality of the final product.

***Batch (or lot*)**

A defined quantity of starting material, packaging material, or product processed in a single process or series of processes so that it could be expected to be homogeneous. In the case of continuous manufacture, the batch must correspond to a defined fraction of the production, characterized by its intended homogeneity. It may sometimes be necessary to divide a batch into a number of sub-batches, which are later brought together to form a final homogeneous batch.

Batch number (or lot number)

A distinctive combination of numbers and/or letters which specifically identifies a batch on the labels, the batch records, the certificates of analysis, etc.

Bio-equivalence

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bioavailability, in terms of peak (Cmax and Tmax) and total exposure (area under the curve (AUC)) after administration of the same molar dose under the same conditions, are similar to such a degree that their effects can be expected to be essentially the same.

Bioavailability

The rate and relative amount of the administered drug which reaches the general circulation intact, or the rate and extent to which the API is absorbed from a drug product and becomes available at the site(s) of action.

Biological Products

Vaccines, immunizer, antigens, hormones, cytokines, enzymes, and other products.

BCS (Biopharmaceutics Classification System) highly soluble

An API for which the highest dose included in the List of Essential Medicines (if the API appear in the List of Essential Medicines) or, the highest dose strength available on the market as an oral solid dosage form is soluble in 250 ml or less of aqueous media over the pH range of 1.2–6.8 at 37ºC.

Bulk Product

Any product that has completed all processing and steps up to, but not including final packaging.

Clinical trial

Any systematic study on pharmaceutical products in human subjects whether in patients or non-patient volunteers in order to discover or verify the effects of, and/or identifies any adverse reaction to investigational products, and/or to study absorption, distribution,

metabolism, and excretion of the products with the object of ascertaining their efficacy and safety.

Commitment batches

Production batches of an API or finished pharmaceutical product (FPP) for which the stability studies are initiated or completed post-approval through a commitment provided with the application.

Comparator product

A pharmaceutical product with which the generic product is intended to be interchangeable in clinical practice. The comparator product will normally be the innovator product for which efficacy, safety, and quality have been established.

Container

That which holds the article and is or may be in direct contact with the drug.

Critical process

A process that may cause variation in the quality of the pharmaceutical product.

Cross-contamination

Contamination of a starting material, intermediate product, or finished product with another starting material or product during production.

Counterfeit Medicine

Means a medicine that is deliberately and fraudulently mislabeled with respect to identity for source. Counterfeit products may be branded or generic medicines, and may include products with the correct ingredients, with the wrong ingredient, without ingredients, with insufficient active ingredient, or with fake packaging material.

Dosage Form

Formulation of an active ingredient(s) so that it can be administered to a patient in specified quantity/strength, e.g., tablets, capsules, injection solution, syrups, ointments, suppositories, etc. "Pharmaceutical Form" and "Finished Product" are synonymous to "Dosage Form.

Drug Master File

A drug master file (DMF) is 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 product such as a container.

Drug Substance

Another term used for the Active Pharmaceutical Ingredient.

Established multisource (generic) product

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

Excipient

Any component of a finished dosage form other than the claimed therapeutic ingredient or active ingredients.

Finished Pharmaceutical Product (FPP)

A finished dosage form that has undergone all stages of manufacture, including packaging in its final container and labelling. Related terms – Intermediate Product, Bulk Product.

Generic Products

The term generic product means a pharmaceutical product, usually intended to be interchangeable with the innovator product, which is usually manufactured without a licence from the innovator company and marketed after expiry of the patent or other exclusivity rights.

Intermediate product

Partly processed product that must undergo further manufacturing steps before it becomes a bulk product.

Immediate Container

That part of a product container which is in direct contact with the drug at all times.

Innovator pharmaceutical product

Generally, the pharmaceutical product that was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety, and quality.

Labeling

Includes any legend, word, or mark attached to, included in, belonging to, or accompanying any drug including: 1) the immediate container label; 2) cartons, wrappers, and similar items; 3) information materials, such as instructional brochures and package inserts.

Manufacturer

A company that carries out operations such as production, packaging, repackaging, labeling, and relabeling of products.

Manufacture

All operations of purchase of materials and products, production, packaging, quality control, release, storage, shipment of finished products, and the related controls.

Manufacturing process

The transformation of starting materials into finished products (drug substances or pharmaceutical dosage forms) through a single operation or a sequence of operations involving installations, personnel, documentation and environment.

Marketing authorization

An official document issued for the purpose of marketing or free distribution of a product after evaluation of safety, efficacy, and quality of the product.

Master formula (MF)

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

Multisource (generic) pharmaceutical products

Pharmaceutically equivalent or pharmaceutical alternative products that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

Officially recognized pharmacopoeia (or compendium)

Those pharmacopoeias recognized by the Authority, i.e., The International Pharmacopoeia (Ph.Int.), European Pharmacopoeia (Ph.Eur.), British Pharmacopoeia (BP), Japanese Pharmacopoeia (JP), and the United States Pharmacopeia (USP).

Ongoing stability study

The study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm, and extend the projected re-test period (or shelf-life) of the API, or to confirm or extend the shelf-life of the FPP.

Pharmaceutical equivalents

Products are pharmaceutically equivalent if they contain the same amount of the same active ingredient(s) in the same dosage form, if they meet the same or comparable standards, and if they are intended to be administered by the same route.

Pilot-scale batch

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

Primary batch

A batch of an API or FPP used in a stability study from which stability data are submitted in a registration application for the purpose of establishing a re-test period or shelf-life.

Production batch

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

Production

All operations involved in the preparation of a pharmaceutical product, from receipt of materials, through processing and packaging, to completion of the finished product.

Packaging material

Any material, including printed material, employed in the packaging of a pharmaceutical product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Packaging

All operations, including filling and labeling, that a bulk product has to undergo in order to become a finished product. Sterile filling would not normally be regarded as part of packaging, the bulk product being the filled, but not the finally packaged, primary container.

Standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g., equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master and batch production documentation.

Specification

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

Stability

The ability of an active ingredient or a drug product to retain its properties within specified limits throughout its shelf-life. The chemical, physical, microbiological, and biopharmaceutical aspects of stability must be considered.

Validation protocol (or plan)

A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process or a part thereof for routine use.

Validation

The demonstration, with documentary evidence, that any procedure, process, equipment, material, activity, or system actually leads to the expected results.

Validation report

A document in which the records, results and evaluation of a completed validation program are assembled. It may also contain proposals for the improvement of processes and/or equipment.

Variation

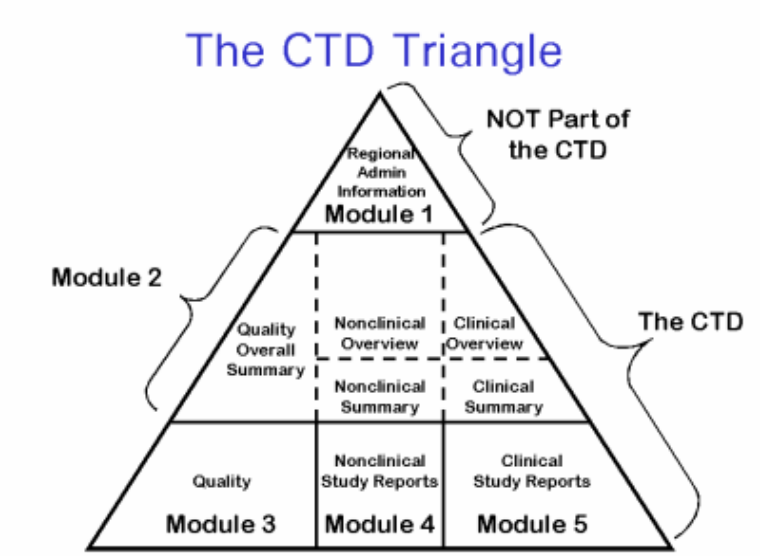
A change to any aspect of a pharmaceutical product including, but not limited to, a change to formulation, method, and site of manufacture or specifications for the finished product, ingredients, container and container labeling, product package (design, color, etc.) and product information.

ICH

The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human use.

BACKGROUND

ECOWAS recognizing that all the fifteen member states have different requirements for submission of their dossiers for the granting of marketing authorization, initiated activities to harmonize medical products registration in the region. This initiative resulted in the development of registration requirements based on CTD format that were validated, and adopted by ECOWAS member states. A Common Technical Document (CTD) is an internationally agreed upon format for the organization and preparation of application dossiers for marketing authorization developed through the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human use (ICH) process, it is used by an increasing number of regulatory authorities, including the European Union, the US Food and Drug Administration, Japan, and Canada among others. The WHO has adopted the CTD as the format for applications submitted to its Prequalified Programme. The CTD is organized into five modules (see the CTD triangle below). Module 1 is region specific and modules 2, 3, 4 and 5 are intended to be common for all regions. Applicants should not modify the overall organization of the CTD.



INTRODUCTION

The regulation of medicines and related health products in Liberia is governed by the provisions and requirements of the Liberia Medicines and Health Products Regulatory Authority (LMHRA) Act, 2010.

The law requires that all medicines manufactured, imported or exported, distributed, or sold in Liberia should be of acceptable quality, safe and efficacious. The process of medicines registration forms an important basis for evaluating and assuring that medicines and health products are of good quality and safe. Mindful of the need to increase access to quality medicines and to promote and protect public health by developing regulatory systems that satisfy minimum regulatory capacity, the Liberia Medicines and Health Products Regulatory Authority has adopted the Common Technical Document format for submission of documentation for registration of pharmaceuticals for human use in Liberia.

Objective

These guidelines are intended to provide guidance to applicants to prepare product dossiers in CTD format for submission to LMHRA.

LEGAL BASIS

In pursuance of Part 1 Section 1 of the Act to Establish the Liberia Medicines and Health Products Regulatory Authority (LMHRA) of 2010, these guidelines, which require use of the Common Technical Document (CTD) format shall be followed by all applicants when preparing applications for Marketing Authorization of Pharmaceutical Products for Human use intended for submission to LMHRA. This guideline is hereby made to provide guidance to applicants on the procedure for registering medicines and health products in Liberia. Applicants are required to familiarize themselves with this document and the above law before completing the registration application form (Appendix 1)

Scope

These guidelines apply to all pharmaceutical products of synthetic or semi-synthetic origin other than biological products, traditional medicinal products, diagnostic aids and medical appliances.

PROCEDURE FOR SUBMISSION OF APPLICATIONS IN CTD FORMAT

All applications should be submitted in:

- English
- Electronic submission of dossiers on a Flash disk in PDF
- Summaries in word format
- Confirm that the electronic submission has been checked with up-to-date and state-of-the-art antivirus software along with duly sign commitment that the submission is free from any form of virus

Applications shall be accompanied by:

- A duly signed covering letter
- Completed applications form in accordance with the sequence of appendices and shall be dated, signed and stamped by the applicant/license holder.
- Samples of the product in the final packaging as specified in Samples Schedule (Sample of Comparator Product should be submitted for all generic formulation)
- Reference or working standard for Active Pharmaceutical Ingredient and related impurities where necessary.
- All supporting documents (Product Dossier) as specified in accordance with the CTD format
- A separate application is required for each product with the same pharmaceutical ingredient but varies in strength and dosage form. The following products will be regarded as either being the same product or separate product applications.
- The summaries (Quality Information Summary (QIS), Quality Overall Summary (QOS), Bioequivalence Trial Information and Bio Waiver Application Form) should be formatted as word document and the body data in pdf format.

TYPES OF APPLICATIONS

#	Type of Application	Applications	
		Same	Separate
1	Each individual dosage form of a particular medicine		X
2	Variations of the active pharmaceutical ingredient (API) of a product		X
3	Tablets/Capsules/Suppositories/Lozenges		X
4	Different pack-sizes of exactly the same strength and Formulation		X
5	Different strengths and formulations.		X
6	Uncoated and coated tablets of the same strength and formulation.		X
7	Syrups/Liquids/Solutions (excluding parenteral) /Creams/ Ointments different container sizes of the same strength and formulation.	X	
8	The same container size of different strengths and formulations. Ampoules and Vials and Large Volume Parenteral		X
9	Different strengths and formulations.		X
10	Uncoated and coated tablets of the same strength and formulation.		X
11	Syrups/Liquids/Solutions (excluding parenteral) /Creams/ Ointments different container sizes of the same strength and formulation.	X	
12	The same container size of different strengths and formulations. Ampoules and Vials and Large Volume Parenteral		X
13	Ampoules or single dose vials containing identical solutions of the same strength but of different volumes (i.e. resulting in different total doses).		X

14	Ampoules containing solutions of different strengths.		X
15	Ampoules and single dose vials containing e.g. dry powder, crystals of different mass		X
16	Ampoules containing “water for injection”, but of different volumes.	X	
17	Special ampoules of dry powder and “water for injections” contained in the same unit, but intended for mixing at the time of injection if water for injections is fully described in dossier	X	
18	Ampoules containing identical solutions of different volumes used only as diluents in the reconstitution of a preparation for parenteral use.	X	
19	Multidose vials containing different volumes of the same strength and formulation with the same dosage schedule.	X	
20	Multidose vials and a single dose ampoule or vial of the same formulation if the single-dose ampoule or vial corresponds to the dose indicated for the Multidose vial.	X	
21	Multidose vials containing dry powder of different mass of the same formulation, and the same concentration when reconstituted.	X	
22	An ampoule of diluents packed together with any preparation including biological medicines if diluent is fully described in dossier.	X	
23	Infusion solutions of the different volumes and of the same formulation which are packed in containers of exactly the same type of material depending on the relevant information submitted.	X	
24	Infusion solutions of the same formulation and of the same or different volume which are packed in containers made of different types of materials.	X	

25	A preparation, packed in plastic containers, intended to be marketed in glass containers containing the same volume and the same formulation.	X	
26	Products with the same strength and formulation but with different colors and/or flavors.		X
27	Applications containing the same API(s) applying for additional indications which render the product in a different scheduling status, or different pharmacological classification, or have any other restrictions imposed other than the original application.		X
28	Removal of antimicrobial preservative from single dose presentation of registered vaccine that included a preservative in the original approved formulation		X
29	Same formulation with different proprietary names whether of the same or different applicants		X

Application for the registration of Pharmaceuticals Products shall be made only by:

- The manufacturer
- A distributor authorized by the manufacturer, license/patent holder
- An authorized Local Agent or Technical Representative (Registered Pharmacist) of the manufacturer

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

Payment of Fees

- All application shall be accompanied by non-refundable registration fee as specified in fee schedule
- All registration shall be accompanied by non-refundable maintenance fee as specified in fee schedule
- All registered/approved products shall be subjected to premarket analysis and applicants are require to pay the applicable fee as specified in fee schedule
- All application submitted to LMHRA for registration of Pharmaceutical Products for human use shall be accompanied by Pharmacovigilance Plan or Risk Management Plan prior to granting Marketing authorization (no fees attached to this plan)

Criteria for rejection of application submission

Rejection at reception: All applications submitted to the Authority shall be subjected to the provisions of these guidelines otherwise the application shall be rejected and applicant notified immediately however the applicant shall have fifteen (15) working days to re-submit the application in line with all submission requirements as specified in the guidelines. Nonconformity to the above shall be given additional fifteen (15) working days, failure to comply, the application will be cancelled and applicant will be required to re-apply and pay all necessary fees.

Rejection after screening and assessors review: Applicant will be notified on the status of their application depending on the submission type either Fast Track or Regular. Assessors Queries will be formulated in to questionnaires communicated to manufacturer of the medicinal product. The applicant is given ninety (90) days to respond to all the queries. Failure to adequately provide answers to the queries the Product will be rejected.

General format and guidance for preparation of dossiers

The CTD is organized into five *modules*; Module 1 is specific to the regulatory Authority of Liberia which includes Administrative and Product information. Modules 2, 3, 4, and 5 are intended to be common for all situations.

The following Modular format of PDs in the CTD content should always be considered during dossier preparation for registration submission to the Authority:

Module 1 – Administrative information and prescribing information
1.1 Cover Letter
1.2. Table of Contents of the Application, including Module 1 (Modules 1-5)
1.3. Application Form
1.4 Correspondence
1.5 Administrative Information
1.6 Regional Summaries
1.6.1 Certificate of Suitability (CEP), if any
1.6.2 Good Manufacturing Practice Certificate and Certificate of Pharmaceutical Product
1.7 Product Information
1.7.1. Summary of Product Characteristics
1.7.2. Labeling Information (immediate and outer label)
1.7.3. Patient Information Leaflet (PIL)
1.8. Evidence of LMHRA Application Fee (Payment Receipts)
Module 2 – Dossier Overall Summary of Product Dossier (DOS-PD)

2.1 PD Table of Contents (Modules 2-5)
2.2 CTD Introduction
2.3 Quality Overall Summary of Product Dossier (QOS-PD)
2.3.S Drug Substance
2.3.P Finished Pharmaceutical Product
2.3.A Appendices
2.3.R Regional Information
2.4 Nonclinical Overview – generally not applicable for multisource products (some exceptions may apply)
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries – generally not applicable for multisource products (some exceptions may apply)
2.7 Clinical Summary – generally not applicable for multisource products
Module 3 – Quality
3.1 Table of Contents of Module 3
3.2.S Body of Data - Drug Substance
3.2.P Body of Data – Finished Drug Product (name, dosage form)
Module 4 – Nonclinical Study Reports – generally not applicable for multisource products (some exceptions may apply)
4.1 Table of Contents of Module 4
4.2 Study Reports
4.3 Literature References
Module 5: Clinical Summaries
5.1 Table of Contents of Module 5
5.2 Tabular Listing of all Clinical Studies
5.3 Clinical Study Reports
5.3.1Reports of Biopharmaceutical Studies (mainly BE study reports for generic products)
5.3.7 Literature References
REFERENCES:
ANNEX A: PRODUCT LABELLING GUIDANCE
Module 1.3.1 Summary of Product Characteristics (SmPC)

Module 1.3.2 Patient Information Leaflet
Module 1.3.3 Container Labeling (Inner and Outer Labels)
ANNEX B: FORMS
B.1 MODEL COVER LETTER LINK
B.2 MODEL APPLICATION FORM FOR DRUG MARKET AUTHORIZATION
B.3 MODEL LETTERS OF ACCESS
B.4 MODEL FEE FORM

MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

1.1.Covering Letter

Dated and signed letter for submission of the dossier by mentioning the product included in the dossier from the manufacturer and/or local agent responsible for registration.

1.2. Table Contents of Modules 1 to 5

Table of contents of Module 1 through Module 5 (of the PD) should be provided in Module 1.

1.3. Application Form

Completed and signed application form as provided in these Guidelines should be submitted. The date of application should correspond to the date of submission of the registration dossier to the Authority.

Good Manufacturing Practice and Certificate of Pharmaceutical Product

A Good Manufacturing Practice (GMP) Certificate and Certificate of Pharmaceutical Product (CPP) issued by a competent authority in the exporting country should be provided in Module 1.

Certificate of Suitability (CEP), if applicable

A complete copy of the Certificate of Suitability (CEP), including any annexes, should be provided in *Module 1.* The declaration of access for the CEP should be duly filled out by the CEP holder on behalf of the FPP manufacturer or applicant to the Authority.

In addition, a written commitment should be included that states the applicant will inform the Authority in the event that the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP will require additional consideration of the API data requirements to support the PD. The written commitment should accompany the copy of the CEP in Module 1.

Along with the CEP, the applicant should supply the following information in the dossier, with data summarized in the DOS-PD and Module 3 of the dossier:

- *3.2. S.1.3 General properties* – discussion of any additional applicable physicochemical and other relevant API properties that are not controlled by the CEP and Ph.Eur. Monograph, e.g. solubility and polymorphs.
- *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.
- *3.2.S.4.1 Specification* – the specifications of the FPP 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.4.2 / 3.2.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 one pilot scale, demonstrating compliance with the FPP manufacturer's API 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.

Product information

Product information including package insert, labeling, and Summary of Product Characteristics (SmPC) should be provided in Module 1 of the dossier. All product information label statements are required to be in English. Any information appearing in the product information (labels, PIL, and SmPC) should be based on scientific justification.

Labeling (immediate and outer label)

Only original labels or computer-ready color-printed or indelible ink labels are accepted for final approval. In the case where the text of the labels is printed directly on plastic bottles through a silk screen process, photocopies of these labels will be accepted for approval.

The titles for batch number, manufacturing, and expiry dates should be part of the printing (typewritten materials, stickers, etc., are not acceptable). If the labeling technology of the manufacturer is such that this information is to be printed on the label during production, a written commitment to show all the required information on the label of the finished product must be submitted. The contents of the label should at least contain:

a) The name of the product– brand and generic/International Non-proprietary Name
b) Pharmaceutical form and route of administration;

c) Qualitative and quantitative composition of active ingredient(s), preservative(s), and antioxidant (s);
d) The volume of the contents, and/or the number of doses, or quantity in container;
e) Directions to consult the package insert or the carton label for complete directions for use;
f) Handling and storage conditions;

g) Batch/Lot number;
h) Manufacturing date;

i) Expiry date; and,
j) Name and full address of manufacturer.

Registration status

Registration status within ECOWAS countries and with Stringent Drug Regulatory Authorities

Evidence of API and/or FPP prequalified by WHO

If an evidence indicating that the active pharmaceutical ingredient and/or finished pharmaceutical products are prequalified by WHO is available, it should be presented in Module 1.

Manufacturing and Marketing authorization

Submit a valid Certificate of Pharmaceutical Product in format recommended by the World Health Organization together with a valid Manufacturing Authorization for pharmaceutical production.

Variation Principles

Variations are changes that may have minor or major effects on the overall safety, efficacy and quality of the product. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application. Such variations can be implemented if no objection letter has been issued within a time period. Should questions arise during the specified period; the change can only be implemented on receipt of a letter of approval from LMHRA.

Please note: patent rights are highly considered like package color, size, applicable pictorials (not more than two), package presentation (size, color, labeling, etc.), administration variation, composition, shelf life or storage and name.

NB// Refer to application form for more details.

PRODUCT REGISTRATION APPLICATION FORM FOR VARIATION

SEC	**DETAIL: APPLICATION NUMBER: DATE RECEIVED:**
1	**Applicant**
	Name of Applicant: _____ Premises/Business Address _____ _____ Telephone: _____ Email: _____ Website: _____

	Name of Local Agent _____ Premises/Business Address _____ _____ Telephone: _____ Email: _____ Website: _____	
	Name of Manufacturer _____ Premises/Business Address _____ _____ Telephone: _____ Email: _____ Website: _____	
	Country of Origin	
2	**STATUS OF APPLICANT (mark as X)**	
	Manufacturer ☐ Importer ☐ Government Agency ☐ Donor Ag ☐ Hospital ☐ Local A ☐ Other (Please Specify) _____	
3	**PRODUCT**	
	Name of Product Proprietary Name Generic Name International Non-Proprietary Name (INN)	**Promotional Category (mark X)** Prescription Only Medicines (POM) ☐ Pharmacy Recommended Medicines (PM) ☐ Over The Counter Medicines (OTC) ☐ Controlled Drug ☐

<table>
<tr><td></td><td>Registration in Country of Origin</td><td>Yes ☐ No ☐</td></tr>
<tr><td></td><td>List of Countries in which product is registered or awaiting registration (attached sheet where necessary)</td><td>1.
2.
3.</td></tr>
<tr><td>4</td><td>PHARMACOLOGICAL CLASSIFICATION</td><td></td></tr>
<tr><td>5</td><td>INDICATIONS</td><td></td></tr>
<tr><td>6</td><td>REASON(S) FOR VARIATION(S)</td><td></td></tr>
<tr><td>7</td><td>AREA(S) OF VARIATION(S)</td><td></td></tr>
<tr><td>8</td><td>PRESENTATIONS & PACKAGING</td><td></td></tr>
<tr><td>9</td><td>DOSAGE FORMS AND SPECIFICATION</td><td></td></tr>
<tr><td>10</td><td colspan="2">NAME & QUANTITY OF EACH INGREDIENT
<table>
<tr><th>No.</th><th>Ingredient</th><th>Specification</th><th>Strength</th></tr>
<tr><td>1</td><td></td><td></td><td></td></tr>
<tr><td>2</td><td></td><td></td><td></td></tr>
<tr><td>3</td><td></td><td></td><td></td></tr>
</table></td></tr>
</table>

A	Additional raw materials (if any) used in the manufacturing process but **NOT** present in the final product	
B	Give specification of packaging materials (where no specifications for packaging materials exist, this must be mentioned).	
C	List any ingredient likely to cause dependance or listed in the United Nations list of psychotropic and narcotic substances	

Reference to the following publications will, where applicable be accepted:

i. British pharmacopoeia
ii. European pharmacopoeia
iii. United States pharmacopoeia
iv. International pharmacopoeia
v. British pharmacopoeia Codex
vi. Martindale's Extra pharmacopoeia
vii. Any other works of reference as may be approved by the Authority from time to time

11	**CHEMICAL NAME & STRUCTURAL FORMULAR OF EACH ACTIVE INGREDIENT**	
	Chemical Name:	
	Empirical Formula:	
	Molecular Weight:	
	Structural Formula:	

12	- **Requirements**	
	- **Batch processing**	
	- **In – Process Checks**	
	- **Packaging Operation**	
13	**Route of Administration**	- Oral ☐ - Intravenous ☐ - Intramuscular ☐ - Topical ☐ - Inhalation ☐ Others (specify) _____
14	**ADVERSE EFFECTS & CONTRA-INDICATION**	
	Adverse Effects	
	Drug Interactions	
	Precautions & Warning	
	Use in Pregnancy and Nursing Mothers	
	Contra-indications	
15	**TREATMENT/ANTIDOTE IN THE EVENT OF OVERDOSE**	

16	**TERATOGENICITY**	
	Pregnancy	
	Development Toxicity	
17	**ANALYTIC METHODS**	
	Specification & Test Methods of Active Ingredients	
	Specification & Test Methods of Excipients	
	Specification & Test Methods of Finished Products	
18	**DECLARATION**	

I the undersigned certify that the information in the accompanying documentation concerning the application for registration of the Medicine or health product indicated hereinis correct and true, and reflects the total information available.

I further certify that I have examined the statements made in this form and I attest to their accuracy. I further confirm that the information referred to in my application file is available for verification. I also agree that I am obliged to comply with the requirements of the Authority related to the stated product at any time in the future.

Name:
_____

Signature:
_____

Position in Company: _____

Date:
_____

STAMP/SEAL

ANNEX I: APPLICATION FORM

LIBERIA MEDICINES AND HEALTH PRODUCTS REGULATORY AUTHORITY

A. Type of application (check the box applicable)

New Application	☐
Periodic re-registration	☐
Variation to existing marketing authorization (If selected, complete the information below.)	☐
• Previous registration number	
• Previous registration condition	
• Brief description of change intended	
• Reasons for variations	

B. Details on the product

Proprietary name (trade name)	
Approved generic name (s) (use INN if any)	
Standard claimed (BP, Ph.In, Ph. Eur., USP, IP, etc.)	
Strength(s) per dosage unit	
Dosage form	
Route of administration	
Shelf life (months)	
Storage condition	
Visual description	

Description of container closure			
Packaging and pack size			
Therapeutic category			
Use category	Scheduled Narcotic□		
	Prescription only□		
	Hospital use only□		
	Pharmacy □		
	Over-the-counter (OTC)□		
Complete qualitative and quantitative composition (indicate per unit dosage form, e.g., per tablet, per 5ml, etc.)** ** Add/delete as many rows and columns as needed.	Composition	Strength	Specification
Complete qualitative and quantitative composition (indicate per batch in Kg, L, etc.)	Composition	Strength	Specification
Statement of similarity and difference of clinical, bio-batch, stability, validation, and commercial batch sizes			
Regulatory situation in other country (Provide a list of countries in which this			

product has been granted a marketing authorization and the restrictions on sale or distribution, e.g., withdrawn from the market, etc.)	

C. Details on the applicant

Name	
Business address	
Street number and postal address	
Telephone number	
Fax number	
E-mail and website address	
Contact person in a company	Name:
	Position:
	Postal address:
	Telephone number:
	Fax number:
	E-mail:
Details of Manufacturer, if different from above	<<Insert the required information as indicated above>>>

D. Details on active pharmaceutical(s) ingredient(s) manufacturer

Name of manufacturer	
Street and postal address	
Telephone/Fax number	
E-mail	
Retest period/Shelf life	

E. Details on local agent (representative) in LIBERIA

Name of local agent	
Sub-city and postal address	
Telephone/Fax number	
E-mail	
Contact person in company Address of company	

F. Details on dossiers submitted with the application

Section of dossier	**Annex, page number, etc.**
Module 1	
Module 2	
Module 3	
Module 4	
Module 5	

CERTIFICATION BY A RESPONSIBLE PERSON IN THE APPLICANT COMPANY

I, the undersigned, certify that all the information in the accompanying documentation concerning an application for a marketing authorization for:

Proprietary name (trade name)	
Approved generic name(s) (INN)	
Strength(s) per dosage unit	
Dosage form	
Applicant	
Manufacturer	

… is correct and true, and reflects the total information available.

I further certify that I have examined the following statements and I attest to their accuracy.

1. The current edition of the WHO Guideline, —Good manufacturing practices for pharmaceutical products, is applied in full in all premises involved in the manufacture of this product.

2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record forms.

3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record forms.

4. Each batch of all starting materials is either tested or certified against the full specifications in the accompanying documentation and comply fully with those specifications *before it is released for manufacturing purposes.*

5. All batches of active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.

6. No batch of active pharmaceutical ingredient will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.

7. Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications *before it is released for manufacturing purposes.*

8. Each batch of the finished product is either tested or certified against the full specifications in the accompanying documentation and complies fully with the release specifications *before it is released for sale.*

9. The person releasing the product for sale is an authorized person as defined by the WHO guideline —Good manufacturing practices: Authorized person - the role, functions and training.

10. The procedures for control of the finished product have been validated for this formulation.

11. The market authorization holder has a standard operating procedure for handling adverse reaction reports on its products.

12. The market authorization holder has a standard operating procedure for handling batch recalls of its products.

13. All the documentation referred to in this Certificate is available for review during a GMP inspection.

14. Any clinical trials including bioequivalence study were conducted according to WHO's —Guidelines for good clinical practice (GCP) for trials on pharmaceutical products.

Signature _____

Name _____

Position in company (print or type) _____

Date: _____

MODULE 2: OVERVIEW & SUMMARIES

2.1 Quality overall summary (QOS)

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

The QOS should include sufficient information from each section to provide the quality assessor with an overview of Module 3. The QOS should also emphasize critical key parameters of the product and provide, for instance, justification in cases where guidelines were not followed. The QOS should include a discussion of key issues that integrates information from sections in the Quality Module and supporting information from other Modules (e.g. qualification of impurities via toxicological studies), including cross-referencing to volume and page number in other Modules.

Template for Quality Overall Summary – Product Dossier) should be completed for generic pharmaceutical products containing APIs of synthetic or semi synthetic origin and their corresponding FPPs.

All sections and fields in the QOS-PD template that would be applicable should be completed. It is understood that certain sections and fields may not apply and should be indicated as such by reporting “not applicable” in the appropriate area with an accompanying explanatory note.

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

2.2 Non-Clinical overview

The non-clinical overview should provide an integrated overall analysis of the information in the Common Technical Document. In general, the Non-clinical Overview should not exceed about 30 pages.
The non-clinical overview should be presented in the following sequence:

- Overview of the non-clinical testing strategy
- Pharmacology
- Pharmacokinetics
- Toxicology
- Integrated overview and conclusions
- List of literature references

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

The Integrated Overview and Conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the non-clinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the non-clinical findings for the safe human use of the pharmaceutical should be discussed (i.e., as applicable to labeling).

Refer to ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part. For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

2.3 Clinical overview

The Clinical Overview is intended to provide a critical analysis of the clinical data in the Common Technical Document. The Clinical Overview will necessarily refer to application data provided in the comprehensive Clinical Summary, the individual clinical study reports (ICH E3), and other
relevant reports; but it should primarily present the conclusions and implications of those data, and should not recapitulate them. Specifically, the Clinical Summary should provide a detailed factual summarization of the clinical information in the CTD, and the Clinical Overview should provide a succinct discussion and interpretation of these findings together with any other relevant information. The clinical Overview should be presented in the following sequence

2.3.1 Product Development Rationale

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

a) Identify the pharmacological class of the FPP.
b) Describe the particular clinical/pathophysiological condition that the FPP is intended to treat, prevent, or diagnose (the targeted indication).
c) Briefly summarize the scientific background that supported the investigation of the FPP for the indication(s) that was (were) studied.
d) Briefly describe the clinical development program of the FPP, including ongoing; and
e) Note and explain concordance or lack of concordance with current standard research approaches regarding the design, conduct and analysis of the studies. Pertinent published literature should be referenced.

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

2.3.2 Overview of Bio-pharmaceutics

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

2.3.3 Overview of Clinical Pharmacology

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

a) Pharmacokinetics, e.g., comparative PK in healthy subjects, patients, and special populations; PK related to intrinsic factors (e.g., age, sex, race, renal and hepatic impairment) and to extrinsic factors (e.g., smoking, concomitant drugs, diet); rate and extent of absorption; distribution, including binding with plasma proteins; specific metabolic pathways, including effects of possible genetic polymorphism and the formation of active and inactive metabolites; excretion; time-dependent changes in pharmacokinetics; stereochemistry issues; clinically relevant PK interactions with other FPPs or other substances.

b) Pharmacodynamics, e.g., information on mechanism of action, such as receptor binding; onset and/or offset of action; relationship of favorable and unfavorable pharmacodynamics effects to dose or plasma concentration (i.e., PK/PD relationships); PD support for the proposed dose and dosing interval; clinically relevant PD interactions with other FPPs or substances; and possible genetic differences in response.

c) Interpretation of the results and implications of immunogenicity studies, clinical microbiology studies, or other drug class specific PD studies summarized in section 2.7.2.4 of the Clinical Summary.

2.3.4 Overview of Efficacy

The purpose of this section is to present a critical analysis of the clinical data pertinent to the efficacy of the FPP in the intended population. The analysis should consider all relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. Those studies deemed relevant for evaluation of efficacy should be identified, and reasons that any apparently adequate and well-controlled studies are not considered relevant should be provided.

Prematurely terminated studies should be noted and their impact considered.

The following issues should generally be considered:

a) Relevant features of the patient populations, including demographic features, disease stage, any other potentially important covariates, any important patient populations excluded from critical studies, and participation of children and elderly (ICH E11 and E7). Differences between the studied population(s) and the population that would be expected to receive the FPP after marketing should be discussed.
b) Implications of the study design(s), including selection of patients, duration of studies and choice of endpoints and control group(s). Particular attention should be given to endpoints for which there is limited experience. Use of surrogate endpoints should be justified. Validation of any scales used should be discussed.
c) For non-inferiority trials used to demonstrate efficacy, the evidence supports a determination that the trial had assay sensitivity and justifying the choice of non-inferiority margin (ICH E10).
d) Statistical methods and any issues that could affect the interpretation of the study results (e.g., important modifications to the study design, including endpoint assessments and planned analyses, as they were specified in the original protocol;
e) Support for any unplanned analyses; procedures for handling missing data; and corrections for multiple endpoints).
f) Similarities and differences in results among studies, or in different patient sub-groups within studies, and their effect upon the interpretation of the efficacy data.
g) g) Observed relationships between efficacy, dose, and dosage regimen for each indication, in Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).
h) For products intended for long-term use, efficacy findings pertinent to the maintenance of long-term efficacy and the establishment of long-term dosage. Development of tolerance should be considered.
i) Data suggesting that treatment results can be improved through plasma concentration monitoring, if any, and documentation for an optimal plasma concentration range.
j) The clinical relevance of the magnitude of the observed effects.
k) If surrogate endpoints are relied upon, the nature and magnitude of expected clinical benefit and the basis for these expectations.

l) Efficacy in special populations. If efficacy is claimed with inadequate clinical data in the population, support should be provided for extrapolating efficacy from effects in the general population.

2.3.5 Overview of Safety

The purpose of this section is to provide a concise critical analysis of the safety data, noting how results support and justify proposed prescribing information. A critical analysis of safety should consider:

a) Adverse effects characteristic of the pharmacological class. Approaches taken to monitor for similar effects should be described.
b) Special approaches to monitoring for particular adverse events (e.g., ophthalmic, QT interval prolongation).
c) Relevant animal toxicology and product quality information. Findings that affect or could affect the evaluation of safety in clinical use should be considered.
d) The nature of the patient population and the extent of exposure, both for test drug and control treatments.
e) Limitations of the safety database, e.g., related to inclusion/exclusion criteria and study subject demographics, should be considered, and the implications of such limitations with respect to predicting the safety of the product in the marketplace should be explicitly discussed.
f) Common and non-serious adverse events, with reference to the tabular presentations of events with the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members the test drug and with control agents in the Clinical Summary. The discussion should be brief, focusing on events of relatively high frequency, those with an incidence higher than placebo, and those that are known to occur in active controls or other members.
g) Serious adverse events (relevant tabulations should be cross-referenced from the Clinical Summary). This section should discuss the absolute number and frequency of serious adverse events, including deaths, and other significant adverse events (e.g., events leading to discontinuation or dose modification), and should discuss the results obtained for test drug versus control treatments. Any conclusions regarding causal relationship (or lack of this) to the product should be provided. Laboratory findings reflecting actual or possible serious medical effects should be considered.
h) Similarities and differences in results among studies, and their effect upon the interpretation of the safety data.
i) Any differences in rates of adverse events in population subgroups, such as those defined by demographic factors, weight, concomitant illness, concomitant therapy, or polymorphic metabolism.
j) Relation of adverse events to dose, dose regimen, and treatment duration.

k) Long-term safety.
l) Methods to prevent, mitigate, or manage adverse events.
m) Reactions due to overdose; the potential for dependence, rebound phenomena and abuse, or lack of data on these issues.
n) World-wide marketing experience. The extent of the world wide experience should be briefly discussed:
   - any new or different safety issues identified.
   - any regulatory actions related to safety.
o) Support for the applicability to the new region of data generated in another region, where appropriate (ICH E5).

2.3.6 Benefits and Risks Conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about the bio pharmaceutics, clinical pharmacology, efficacy and safety of the FPP and to provide an overall appraisal of the benefits and risks of its use in clinical practice. Also, implications of any deviations from regulatory advice or guidelines and any important limitations of the available data should be discussed here. This assessment should address critical aspects of the proposed Prescribing Information. This section should also consider the risks and benefits of the FPP as they compare to available alternative treatments or to no treatment in illnesses where no treatment may be a medically acceptable option; and should clarify the expected place of the FPP in the armamentarium of treatments for the proposed indication. If there are risks to individuals other than those who will receive the drug, these risks should be discussed (e.g., risks of emergence of drug-resistant bacterial strains with widespread use of an antibiotic for minor illnesses). The analyses provided in previous sections should not be reiterated here.

This section often can be quite abbreviated when no special concerns have arisen and the drug is a member of a familiar pharmacological class.

This analysis of benefits and risks is generally expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

a) The efficacy of the FPP for each proposed indication.
b) Significant safety findings and any measures that may enhance safety.
c) Dose-response and dose-toxicity relationships; optimal dose ranges and dosage regimens.
d) Efficacy and safety in sub-populations, e.g., those defined by age, sex, ethnicity, organ function, disease severity, and genetic polymorphisms.
e) Data in children in different age groups, if applicable, and any plans for a development program in children.
f) Any risks to the patient of known and potential interactions, including food-drug and drug-drug interactions, and recommendations for product use.

g) Any potential effect of the FPP that might affect ability to drive or operate heavy machinery.
h) Examples of issues and concerns that could warrant a more detailed discussion of benefits and risks might include: The drug is for treatment of a non-fatal disease but has known or potential serious toxicity, such as a strong signal of carcinogenicity, teratogenicity, pro-arrhythmic potential (effect on QT interval), or suggestion of hepatotoxicity.
i) The proposed use is based on a surrogate endpoint and there is a well-documented important toxicity.
j) Safe and/or effective use of the drug requires potentially difficult selection or management approaches that require special physician expertise or patient training

2.3.7 Literature References

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

Refer to ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy (M4E) for guidance on the format and the content of this part.

2.4 Non-clinical Written and Tabulated Summaries

The following order is recommended:

2.4.1 Non-clinical Written Summaries

This guideline is intended to assist authors in the preparation of non-clinical pharmacology, pharmacokinetics, and toxicology written summaries in an acceptable format. This guideline is not intended to indicate what studies are required. It merely indicates an appropriate format for the nonclinical data that have been acquired.

The sequence and content of the Non-clinical Written Summary sections are described below. It should be emphasized that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation of the results.

Whenever appropriate, age- and gender-related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included, as appropriate.

Consistent use of units throughout the Summaries will facilitate their review. A table for converting units might also be useful.

In the Discussion and Conclusion sections, information should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses.

Order of Presentation of Information within Sections

When available, in vitro studies should precede in vivo studies.

Where multiple studies of the same type need to be summarized within the Pharmacokinetics and Toxicology sections, studies should be ordered by species, by route, and then by duration (shortest duration first).
Species should be ordered as follows:

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

Routes of administration should be ordered as follows:

a) The intended route for human use
b) Oral
c) Intravenous
d) Intramuscular
e) Intraperitoneal
f) Subcutaneous
g) Inhalation
h) Topical
i) Other

Use of Tables and Figures

Although the Nonclinical Written Summaries are envisaged to be composed mainly of text, some information contained within them might be more effectively and/or concisely communicated through the use of appropriate tables or figures.

To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries.

Throughout the text, reference citations to the Tabulated Summaries should be included.

Length of Nonclinical Written Summaries

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

Sequence of Written Summaries and Tabulated Summaries

The following order is recommended:

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

2.4.2 Content of Non-clinical Written and Tabulated Summaries

The aim of this section should be to introduce the reviewer to the pharmaceutical and to its proposed clinical use. The following key elements should be covered:

a) Brief information concerning the pharmaceutical‘s structure (preferably, a structure diagram should be provided) and pharmacologic properties.
b) Information concerning the pharmaceutical‘s proposed clinical indication, dose, and duration of use.

2.4.3 Pharmacology Written Summary

a. Tabulated Summary of Pharmacology
b. Written Summary of Pharmacokinetics
c. Tabulated Summary of Pharmacokinetics
d. Written Summary of Toxicology
e. Tabulated Summary of Toxicology
f. Secondary Pharmacodynamics
g. Safety Pharmacology

h. Pharmacodynamics Drug Interactions
i. Discussion and Conclusions
j. Tables and Figures (either here or included in text)

MODULE 3: QUALITY

3.1 Table of Contents of Module 3

A Table of Contents for the filed application should be provided.

3.2. Body of Data

3.2 S Drug Substance 1 (Name, Manufacturer)
3.2 S.1 General Information (Name, Manufacturer)
3.2 S 1.1 Nomenclature (name, manufacturer)

Information on the nomenclature of the drug 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
- The listed chemical names should be consistent with those appearing in scientific literature and those appearing on the product labeling information (e.g., summary of product characteristics; package leaflet, also known as patient information leaflet or PIL; or labeling). Where several names exist, the preferred name should be indicated.

3.2 S.1.2 Structure (name, manufacturer)

The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

For bio-tech drug substance, the schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate.

3.2 S.1.3 General properties (name, manufacturer)

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech. (Reference: ICH Guidelines Q6A and Q6B)

This information can be used in developing the specifications, in formulating FPPs, and in testing for release and stability purposes. The physical and chemical properties of the API should be discussed, including the physical description, solubility in common solvents (e.g., water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g., pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygrocopicity, partition coefficient, etc. (See table in the DOS-PD). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

3.2 S.2 Manufacture (Name, Manufacturer)

3.2 S.2.1 Manufacturer(s) (name, manufacturer)

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 list of manufacturers/companies should specify the actual addresses of production or manufacturing site(s) involved (including block(s) and units(s)), rather than the administrative offices. Telephone number(s), fax number(s) and e-mail address(es) should be provided.

A valid manufacturing authorization should be provided for the production of APIs. If available, a certificate of GMP compliance should be provided in the PD in Module 1.

3.2 S.2.2 Description of manufacturing process and process controls (name, manufacturer)

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For a synthetic drug substance, a flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions and solvents.

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

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

Where possible, and for confidentiality reasons, the holder of the APIMF can submit the restricted part of the APIMF to the Authority. In this case, if detailed information is presented in the restricted part, the information to be provided for this section of the applicant FPP 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 APIs, 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).

For biotech drug substance, information should be provided on the manufacturing process, which typically starts with a vial(s) of the cell bank, and includes cell culture, harvest(s), purification and modification reactions, filling, storage, and shipping conditions. An explanation of the batch numbering system, including information regarding any pooling of harvests or intermediates and batch size or scale should be provided.

A flow diagram should be provided that illustrates the manufacturing route from the original inoculum (e.g., cells contained in one or more vials(s) of the Working Cell Bank up to the last harvesting operation. The diagram should include all steps (i.e., unit operations) and intermediates. Relevant information for each stage, such as population doubling levels, cell concentration, volumes, pH, cultivation times, holding times, and temperature, should be included. Critical steps and critical intermediates for which specifications are established (as mentioned in 3.2.S.2.4) should be identified.

A description of each process step in the flow diagram should be provided. Information should be included on, for example, scale; culture media and other additives (details provided in 3.2.S.2.3); major equipment (details provided in 3.2.A.1); and process controls, including in-process tests and operational parameters, process steps, equipment and intermediates with acceptance criteria (details provided in 3.2.S.2.4).Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided.(Details on shipping and storage should be provided in 3.2.S.2.4.).

For purification and modification reaction of drug substance, a flow diagram should be provided that illustrates the purification steps (i.e., unit operations) from the crude harvest(s), up to the step preceding filling of the drug substance. All steps and intermediates and relevant information for each stage (e.g., volumes, pH, critical processing time, holding times, temperatures and elution profiles, selection of fraction, and storage of intermediate, if applicable) should be included. Critical steps for which specifications are established (as mentioned in 3.2.S.2.4) should be identified. A description of each process step (as identified in the flow diagram) should be provided.

The description should include information on, for example, scale, buffers, and other reagents (details provided in 3.2.S.2.3), major equipment (details provided in3.2.A.1), and materials. For materials, such as membranes and chromatography resins, information for conditions of use and reuse also should be provided. (Equipment details in 3.2.A.1; validation studies for the reuse and regeneration of columns and membranes in 3.2.S.2.5.) The description should include process controls (including in-process tests and operational parameters) with acceptance criteria for process steps, equipment and intermediates (details in 3.2.S.2.4.).
Reprocessing procedures with criteria for reprocessing of any intermediate or the drug substance should be described. (Details should be given in 3.2.S.2.5.)

Information on procedures used to transfer material between steps, equipment, areas, and buildings, as appropriate, and shipping and storage conditions should be provided (detailson shipping and storage provided in 3.2.S.2.4.).A description of the filling procedure for the drug substance, process controls (including in-process tests and operational parameters), and acceptance criteria should be provided (details in 3.2.S.2.4.). The container closure system(s) used for storage of the drug substance (details in 3.2.S.6.) and storage and shipping conditions for the drug substance should be described. (Reference: ICH Guidelines Q5A, Q5B, and Q6B)

Where polymorphic/amorphous forms have been identified, the form resulting from the synthesis should be stated. Where particle size is considered a critical attribute, the particle size reduction method(s) (milling, micronization) should be described.

Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list, in tabular form, should be provided comparing the processes at each site and highlighting any differences.
3.2 S.2.3 Control of materials (name, manufacturer)

Materials used in the manufacture of the drug 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 (including biologically-sourced materials, e.g., media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate. For biologically-sourced materials, this can include information regarding the source, manufacture, and characterization. (Details in 3.2.A.2)

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

A letter of attestation should be provided confirming that the API and the starting materials and reagents used to manufacture the API are without risk of transmitting agents of animal spongiform encephalopathies. When available, a CEP demonstrating Transmissible Spongiform Encephalopathy (TSE)-compliance should be provided. A complete copy of the CEP (including any annexes) should be provided in Module 1.

3.2 S.2.4 Controls of critical steps and intermediates (name, manufacturer)

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. Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable. Additionally for Biotech: Stability data supporting storage conditions should be provided. (Reference: ICH Guideline Q5C)

3.2 S.2.5 Process validation and/or evaluation (name, manufacturer)

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.
For biotech drug substances, sufficient information should be provided on validation and evaluation studies to demonstrate that the manufacturing process (including reprocessing steps) is suitable for its intended purpose and to substantiate selection of critical process controls (operational parameters and in-process tests) and their limits for critical manufacturing steps (e.g., cell culture, harvesting, purification, and modification).

The plan for conducting the study should be described and the results, analysis and conclusions from the executed study should be provided. The analytical procedures and corresponding validation should be cross-referenced (e.g., 3.2.S.2.4, 3.2.S.4.3) or provided as part of justifying the selection of critical process controls and acceptance criteria.

For manufacturing steps intended to remove or inactivate viral contaminants, the information from evaluation studies should be provided in 3.2.A.2.

3.2 S.2.6 manufacturing process development (name, manufacturer)

A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing comparative bioavailability or bio-waiver, scale-up, pilot, clinical and, if available, production scale batches.

The significance of the change should be assessed by evaluating its potential to impact the quality of the drug substance (and/or intermediate, if appropriate). For manufacturing changes that are considered significant, data from comparative analytical testing on relevant drug substance batches should be provided to determine the impact on quality of the drug substance. A discussion of the data, including a justification for selection of the tests and assessment of results, should be included.

Testing used to assess the impact of manufacturing changes on the drug substance(s)and the corresponding drug product(s) can also include nonclinical and clinical studies. Cross-reference to the location of these studies in other modules of the submission should be included.

3.2 S.3 Characterization (Name, Manufacturer)

3.2 S.3.1 Elucidation of structure and other characteristics (name, manufacturer)

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.

For biotech drug substance for the desired product and product-related substances, details should be provided on primary, secondary, and higher-order structure, post-translational forms (e.g., glycoforms), biological activity, purity, and immunochemical properties, when relevant. [Reference: ICH Guideline Q6B]

Elucidation of structure

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

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

For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) runs concomitantly with a pharmacopoeia reference standard. See Section 3.2.S.5 for details on acceptable reference standards or materials.

Isomerism/stereochemistry

When an API is chiral, it should be specified whether specific stereoisomers or a mixture of stereoisomers have been used in the clinical or the comparative bio-studies, and information should be given as to the stereoisomer of the API that is to be used in the FPP.

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 identically of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity. The potential for inter-conversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.

When a single enantiomer of the API is claimed for non-pharmacopoeia APIs, 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 API, there is no potential for stereoisomerism, it is sufficient to include a statement to that effect.
Polymorphism

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

different arrangements and/or conformations of the molecules in the crystal lattice. Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or 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 API process-ability, pharmaceutical product manufacturability, and product quality/performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

There are a number of methods that can be used to characterize the polymorphic forms of an API. 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 APIs 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 FPP, and to decide whether a preferred polymorph should be monitored at release and on storage of the API. Where there is a preferred polymorph, acceptance criteria should be incorporated into the API specification to ensure polymorphic equivalence of the commercial material and that of the API batches used in the comparative bioavailability or bio waiver studies. The polymorphic characterization of the API batches used in clinical, comparative bioavailability, or bio waiver 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.

Particle size distribution

For APIs that are not BCS highly soluble contained in solid FPPs, or liquid FPPs containing un-dissolved API, the particle size distribution of the material can have an effect on the in vitro and/or in vivo behavior of the FPP. 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 API should be provided, including characterization of the batch (es) used in clinical and in the comparative bioavailability or bio waiver studies. API 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 bio waiver 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. [Reference: ICH Guideline Q6A]

3.2 S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided. [Reference: ICH Guidelines Q3A, Q3C, Q5C, Q6A, and Q6B] Regardless of whether a pharmacopeial standard is claimed, a discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture, or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities, and degradation products and should include the chemical names, structures, and origins. The discussion of pharmacopoeia APIs should not be limited to the impurities specified in the API monograph.

The tables in the DOS-PD template should be used to summarize the information on the API-related and process-related impurities. In the DOS-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 API.

Identification threshold

It is recognized by the pharmacopoeias that APIs can be obtained from various sources and thus can contain impurities not considered during the development of the monograph. Furthermore, a change in the production or source may give rise to additional impurities that are not adequately controlled by the official compendia 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 APIs having a maximum daily dose of ≤2 g/day) are generally recommended, rather than the general limits for unspecified impurities that may appear in the official compendia monograph that could potentially be higher than the applicable ICH limit.

Qualification of impurities

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

The limit for an impurity present in an existing API can be accepted by comparing the impurity results found in the existing API with those observed in an innovator product using the same validated, stability-indicating analytical procedure (e.g., comparative high performance liquid chromatography (HPLC) studies). If samples of the innovator product are not available, the

impurity profile may also be compared to a different comparator (market leading) FPP with the same route of administration and similar characteristics (e.g., tablet versus capsule). It is recommended that the studies be conducted on comparable samples (e.g., age of samples) to obtain a meaningful comparison of the impurity profiles.

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

A specified impurity present in the existing API is considered qualified if the amount of the impurity in the existing API reflects the levels observed in the innovator or comparator (market leading) FPP.

ICH class II solvent(s) used prior to the last step of the manufacturing process may be exempted from routine control in API specifications if suitable justification is provided. Submission of results demonstrating less than 10% of the ICH Q3C limit (option I) of the solvent(s) in three consecutive production-scale batches or six consecutive pilot-scale batches of the API or a suitable intermediate would be considered acceptable justification. The last-step solvents used in the process should always be routinely controlled in the final API. The limit for residues of triethylamine (TEA) is either 320 ppm on the basis of ICH Q3C (option 1) or 3.2 mg/day on the basis of permitted daily exposure (PDE).

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's (e.g., EMEA or USFDA Guidance for Industry: Genotoxic and carcinogenic impurities in drug substances and products, recommended approaches could be applicable.

Residues of metal catalysts used in the manufacturing process and determined to be present in batches of API 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 FPP (e.g., an iron oxide pigment). The guideline on the specification limits for residues of metal catalysts or metal reagents, EMEA 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, WHO Good Distribution Practices for Pharmaceutical Products (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.

3.2 S.4 Control of Drug Substance (name, manufacturer)

3.2 S.4.1 Specification (name, manufacturer)

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

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

- The standard declared by the applicant could be an officially recognized compendial standard (e.g., Ph.Int., Ph.Eur., BP, USP, JP) or a House (manufacturer's) standard.
- The specification reference number and version (e.g., revision number and/or date) should be provided for version control purposes.
- For the analytical procedures, the type should indicate the kind of analytical procedure used (e.g., visual, IR, UV, HPLC, laser diffraction); the source refers to the origin of the analytical procedure (e.g., Ph.Int., Ph.Eur., BP, USP, JP, in-house); and the version (e.g., code number/version/date) should be provided for version control purposes.

In case where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement —for API from manufacturer All (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 APIs. [Reference: ICH Guidelines Q3A, Q3C, Q6A; officially recognized pharmacopoeia]

3.2 S.4.2 Analytical procedures (name, manufacturer)

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

3.2 S.4.3 Validation of analytical procedures (name, manufacturer)

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

Copies of the validation reports for the analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided. Tables should be used to summarize the validation information of the analytical procedures of the FPP manufacturer for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS-PD. 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-PD.

The compendial methods as published are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products that were not considered during the development of the monograph. Therefore, the monograph and compendial method should be demonstrated suitable to control the impurity profile of the API from the intended source(s).

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

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

3.2 S.4.4 Batch analyses (name, manufacturer)

Description of batches and results of batch analyses should be provided. The information provided should include batch number, batch size, date and production site of relevant API batches. Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. This data is used to evaluate consistency in API quality. The FPP manufacturer's test results should be summarized in the QOS-PD.
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 for the API specification

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 (name, manufacturer)

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

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

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeia source (e.g. BP, Ph.Eur, Ph.Int., USP) where one exists and the lot number should be provided. Primary reference standards from officially recognized pharmacopoeia sources do not need further structural elucidation Otherwise a primary standard may be a batch of the API that has been fully characterized (e.g. by IR, UV, NMR, MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water-/solvent-free basis). Absolute content of the primary reference standard must be declared and should follow the scheme: 100% minus organic impurities (quantitated by an assay procedure, e.g. HPLC, DSC, etc.) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

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

3.2 S.6 Container-closure system (name, manufacturer)

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

For non-functional secondary packaging components (e.g. those that do not provide additional protection), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, and/or safety of materials of construction. Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR). Copies of the labels applied on the secondary packaging of the API should be provided and should include the conditions of storage. In addition, the name and address of the manufacturer of the API should be stated on the container, regardless of whether relabeling is conducted at any stage during the API distribution process.

3.2 S.7 Stability

Provide data on Stability Testing of Active Pharmaceutical Ingredients and Finished Pharmaceutical Products in line with method that comply with recognized Compendia.

3.2 P Drug product (or finished pharmaceutical product (FPP)) (name, dosage form)
3.2 P.1 Description and Composition of the FPP (name, dosage form)
A description of the FPP and its composition should be provided. The information provided should include, for example:

a) Description of the dosage form

The description of the FPP should include the physical description, available strengths, release mechanism (e.g. immediate, modified (delayed or extended)), as well as any other distinguishable characteristics.

b) Composition

The list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the ingredients, and a reference to their quality standards [e.g. compendial monographs (BP, USP, Ph. Eur etc) or manufacturer's specifications (IH)].

The tables in the QOS-PD template should be used to summarize the composition of the FPP and express the quantity of each component on a per unit basis (e.g. mg per tablet, mg per ml, mg per vial) and quantity per batch. The individual ingredient for mixtures prepared in-house (e.g. coatings) should be included in the tables, where applicable.

All ingredients 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 FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "contains 2% overage of the API to compensate for manufacturing losses").

The ingredients should be declared by their proper or common names, quality standards (e.g. BP, Ph.Eur, Ph.Int., USP, in-house) and, if applicable, their grades (e.g. "Microcrystalline Cellulose NF (PH 102)") and special technical characteristics (e.g. lyophilized, micronized, solubilized, 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.

a) Description of accompanying reconstitution diluent(s)
For FPPs supplied with reconstitution diluent(s), information on the diluent(s) should be provided in a separate FPP portion ("3.2.P"), as appropriate.

3.2 P.2 Pharmaceutical development (name, dosage form)

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 product dossier. 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 FPP quality. Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical development section. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the product dossier.

Pharmaceutical development information should include, at a minimum:

a) the definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering for example the route of administration, dosage form, bioavailability, strength and stability;
b) identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;
c) discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount to deliver drug product of the desired quality; and
d) discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

These features should be discussed as part of the product development using the principles of risk management over the entire life-cycle of the product.

References:

a) ICH Q8 guidelines: Pharmaceutical Development
b) ICH Q9 guidelines: Quality Risk Management

3.2 P.2.1 Components of the FPP (name, dosage form)

3.2 P.2.1.1 Active pharmaceutical ingredient (name, dosage form)

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

Physicochemical characteristics of the API may influence both the manufacturing capability and the performance of the FPP.

3.2 P.2.1.2 Excipients (name, dosage form)

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

3.2 P.2.2 Finished pharmaceutical product (name, dosage form)
3.2 P.2.2.1 Formulation development (name, dosage form)

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

If the proposed FPP is a functionally scored tablet, a study should be undertaken to ensure the uniformity of dose in the tablet fragments. 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 mass 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.

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.

3.2 P.2.2.2 Overages (name, dosage form)

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).

3.2 P.2.2.3 Physicochemical and biological properties (name, dosage form)

Parameters relevant to the performance of the FPP, 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.

3.2 P.2.3 manufacturing process development (name, dosage form)

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 bio-waiver batches and the process described in 3.2.P.3.3 that can influence the performance of the product should be discussed. 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.

3.2 P.2.4 Container-closure system (name, dosage form)

The suitability of the container-closure system (described in 3.2.P.7) used for the storage, transportation (shipping) and use of the FPP 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 FPP).

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 FPP) should also be discussed.

3.2 P.2.5 Microbiological attributes (name, dosage form)

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. USP or PhEur general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

3.2P.2.6 Compatibility (name, dosage form)

The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, absorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling. Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such reconstitution) that are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

3.2 P.3 Manufacture (name, dosage form)

3.2P.3.1 Manufacturer(s) (name, dosage form)

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.

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

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. This information should be submitted in section 1.9.

3.2 P.3.2 Batch formula (name, dosage form)

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 FPP 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 ingredients 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 FPP 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 = 1.075 kg active ingredient hydrochloride”). All overages should be clearly indicated (e.g. “Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses”).

The ingredients should be declared by their proper or common names, quality standards (e.g. BP, Ph.Eur, Ph.Int., USP, house) and, if applicable, their grades (e.g. “Microcrystalline Cellulose NF (PH 102)”) and special technical characteristics (e.g. lyophilized, micronized, solubilized, emulsified).

3.2P.3.3 Description of manufacturing process and process controls (name, dosage form)

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 3.2.P.3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated. The maximum holding time for bulk FPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptic FPP, the holding time of the filtered product prior to filling should be supported by the submission of stability data, if longer than 24 hours.

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

Provide a copy of the master formula and a copy of a manufacturing record for a real batch.

3.2P.3.4 Controls of critical steps and intermediates (name, dosage form)

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.

3.2P.3.5 Process validation and/or evaluation (name, dosage form)

Description, documentation and results of the validation and/or evaluation 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).

A product quality review may be submitted in lieu of the information below. The following information should be provided:

a) A copy of the process validation protocol, specific to this FPP, that identifies the critical equipment and process parameters that can affect the quality of the FPP and defines testing parameters, sampling plans, analytical procedures and acceptance criteria;
b) A commitment that three consecutive, production-scale batches of this FPP 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.
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.

The process validation protocol should include inter alia the following:

a) a reference to the current master production document;
b) a discussion of the critical equipment;
c) the process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;

d) 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);
e) 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 bio waiver studies;
f) the analytical procedures or a reference to appropriate section(s) of the dossier;
g) the methods for recording/evaluating results; and
h) the proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs 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. 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 FPP will not be affected. Details such as temperature range and peak dwell time for an FPP 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 API 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. Results on microbial contamination levels should be provided.

Note: For an established generic product a product quality review (refer to Annex 11 – Product Quality Review Requirements for Generic Pharmaceutical Products) 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.

3.2P.4 Control of excipients (name, dosage form)
3.2P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided. The specifications from the FPP 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 FPP (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.

If the standard claimed for an excipient is a non-compendial standard (e.g. 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. For oils of plant origin (e.g. soy bean, peanut) the absence of aflatoxins or biocides should be demonstrated.

The colors permitted for use are limited to those listed in the “Japanese pharmaceutical excipients”, the EU “List of permitted food colors”, 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 FPP manufacturer’s specifications for the product including identification testing. For flavors the qualitative composition should be submitted, as well as a declaration that the excipients comply with foodstuff regulations (e.g. USA or EU).

Information that is considered confidential may be submitted directly to LMHRA by the applicant with reference to the specific related product. If additional purification is undertaken on commercially available excipients details of the process of purification and modified specifications should be submitted.

3.2P.4.2 Analytical procedures (name, dosage form)

The analytical procedures used for testing the excipients should be provided where appropriate. Copies of analytical procedures from officially recognized compendial monographs do not need to be submitted.

3.2P.4.3 Validation of analytical procedures (name, dosage form)

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.

3.2P.4.4 Justification of specifications (name, dosage form)

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.

3.2P.4.5 Excipients of human or animal origin (name, dosage form)

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

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If from plant origin a declaration to this effect will suffice. For these excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are without risk of transmitting agents of animal spongiform encephalopathies.

3.2P.4.6 Novel excipients (name, dosage form)

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

3.2P.5 Control of FPP (name, dosage form)

3.2 P.5.1 Specification(s) (name, dosage form)

A copy of the FPP specification(s) from the applicant (as well as the company responsible for the batch release of the FPP, 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 FPP (release) and shelf life monitoring.

The specifications should be summarized according to the tables in the DOS-PD template including the tests, acceptance criteria and analytical procedures (including types, sources and versions for the methods):

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

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 coloring materials, identification and assay of antimicrobial or chemical preservatives (e.g., antioxidants), and microbial limit tests.

The following information provides guidance for specific tests:

- fixed-dose combination FPPs (FDC-FPPs):

  - analytical methods that can distinguish each API in the presence of the other API(s) should be developed and validated,
  - acceptance criteria for degradation products should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, its acceptance limits should be calculated with reference to the worst case (the API 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 API 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 API in the FPP,
  - when all APIs 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 the FPP, in lieu of content uniformity testing;

modified-release products: a meaningful API release method;

- inhalation and nasal products: consistency of delivered dose (throughout the use of the product), particle or droplet size distribution profiles (comparable to the product used in in-vivo studies, where applicable) and if applicable for the dosage form, moisture content, leak rate, microbial limits, preservative assay, sterility and weight loss;
- Suppositories: uniformity of dosage units, melting point;
- Transdermal dosage forms: peal or shear force, mean weight per unit area, dissolution; and,
- Sterile: sterility, endotoxin.

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

Skip testing is acceptable for parameters such as identification of coloring materials and microbial limits, when justified by the submission of acceptable supportive results for five production batches. When skip testing justification has been accepted, the specifications should include a footnote, stating at minimum the following skip testing requirements: at minimum, every tenth batch and at least one batch annually is tested. In addition, for stability-indicating parameters such as microbial limits, testing will be performed at release and shelf-life during stability studies.

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 and moisture content, are normally not accepted. [Reference: ICH Guidelines Q3B, Q3C, Q6A; official monograph]

3.2 P.5.2 Analytical procedures (name, dosage form)

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 routing testing should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendial analytical procedures.

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-PD (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 FPP.

Refer to Section 3.2.S.4.2 of this Guideline for additional guidance on analytical procedures. 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 API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP 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 FPP.

For officially recognized compendial FPP 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.

3.2.P.5.4 Batch analysis (name, dosage form)

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 FPP 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 FPP (generally, the applicant or the FPP manufacturer, if different from the applicant) should be provided for not less than two batches of at least pilot-scale, or in the case of an uncomplicated1 FPP (e.g., immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot-scale and a second batch which may be smaller (e.g., for solid oral dosage forms, 25,000 or 50,000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The testing results should include the batch(s) 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: ICH Guidelines Q3B, Q3C, Q6A; official monograph]

3.2.P.5.5 Characterization of impurities (name, dosage form)

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 API with other APIs (FDCs), excipients, or the container closure system) and FPP process-related impurities (e.g., residual solvents in the manufacturing process for the FPP). [Reference: ICH Guidelines Q3B, Q3C, Q6A]

3.2.P.5.6 Justification of specification(s) (name, dosage form)

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 its location should be provided.

ICH Guideline Q6A should be consulted for the development of specifications for FPPs.

3.2.P.6 Reference standards or materials (name, dosage form)

Information on the reference standards or reference materials used for testing of the FPP should be provided, if not previously provided in —3.2.S.5 Reference Standards or Materials.

Information should be provided on reference materials of FPP degradation products, where not included in 3.2.S.5.[Reference: ICH Guideline Q6A; WHO Technical Report Series, No. 943, Annex 3]

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

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.

The WHO Guidelines on packaging for pharmaceutical products (WHO Technical Report Series, No. 902, Annex 9, 2002) and the officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.

Descriptions, materials of construction and specifications (of the company responsible for packaging the FPP, generally the FPP 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 FPP quality during storage and shipping.

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 (Name, Dosage Form)

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.

Stress testing

Photostability testing should be conducted on at least one primary batch of the FPP, if appropriate. If —protect from light‖ is stated in one of the officially recognized pharmacopoeias for the API or FPP, it is sufficient to state —protect from light‖ on labeling, in lieu of photostability studies, when the container closure system is shown to be light protective. Additional stress testing of specific types of dosage forms may be appropriate (e.g., cyclic studies for semi-solid products, freeze-thaw studies for liquid products).

Accelerated, intermediate (if necessary) and long-term testing

Stability data must demonstrate stability of the medicinal product throughout its intended shelf-life under the climatic conditions of Liberia. Refer to WHO Technical Report Series, No. 953, Annex 2, Appendix 1, for information on climatic zones. According to Annex 2,Appendix 1, the required long-term storage conditions for Liberia is 30ºC±2ºC/65%±5%RH.The minimum long-term storage condition should thus fulfill the storage conditions of 30ºC±2ºC/65%±5%RH, while the more universal condition of 30ºC±2ºC/75%±5%RH, as recommended by WHO, can also be acceptable. The use of alternative long-term conditions will need to be justified and should be supported with appropriate evidence.

Other storage conditions are outlined in the WHO stability guideline for FPPs packaged in impermeable and semi-permeable containers and those intended for storage in a refrigerator and in a freezer. FPPs intended for storage below -20°C should be treated on a case-by-case basis.

Storage temperature (ºC)	Relative humidity (%)	Minimum time period (months)
Accelerated 40±2	75±5	6
Intermediate *	N/A	N/A
Long-term 30±2	65±5 or 75±5	6

**Where long-term conditions are 30ºC±2ºC/65%±5%RH or 30ºC±2ºC/75%±5%RH, there is no intermediate condition.*

To establish the shelf-life, data should be provided on not less than two batches of at least pilot-scale, or in the case of an uncomplicated FPP (e.g., immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot-scale and a second batch which may be smaller (e.g., for solid oral dosage forms, 25,000 or 50,000 tablets or capsules) of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.

The stability testing program should be summarized and the results of stability testing should be reported in the dossier and summarized in the tables in the DOS-PD. Bracketing and matrixing of proportional strengths can be applied, if scientifically justified.

For sterile products, sterility should be reported at the beginning and end of shelf-life, and sub-visible particulate matter should be reported frequently, but not necessarily at every test interval. Bacterial endotoxins need only be reported at the initial test interval. Weight loss from plastic containers should be reported over the shelf-life. In-use periods after first opening of the container closure (e.g., parenteral and ophthalmic products) should be justified with experimental data.

The information on the stability studies should include details such as

- storage conditions;
- strength;
- batch number, including the API batch number(s) and manufacturer(s);
- batch size;
- Container closure system, including orientation (e.g., erect, inverted, on-side), where applicable; and,
- completed (and proposed) test intervals.

The discussion of test 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 and any trends that were observed. 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. Dissolution results should be expressed at minimum as both the average and range of individual results.

Applicants should consult the ICH Q1E guidance document for details on the evaluation and extrapolation of results from stability data (e.g., if significant change was not observed within six months at accelerated condition and the data show little or no variability, the proposed shelf-life could be up to two times the period covered by the long-term data, but should not exceed the long-term data by 12 months).

Proposed storage statement and shelf-life

The proposed storage statement and shelf-life (and in-use storage conditions and in-use period, if applicable) for the FPP should be provided. [Reference: WHO TRS No. 953, Annex 2; ICH Guidelines Q1A, Q1B, Q1C, Q1D, Q1E, Q3B, Q6A]

3.2. P.8.2 Post-approval stability protocol and stability commitment (name, dosage form)

Primary stability study commitment

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

Commitment stability studies

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

Ongoing stability studies

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

Any differences in the stability protocols used for the primary batches and those proposed for the commitment batches or ongoing batches should be scientifically justified.

3.2.P.8.3 Stability data (name, dosage form)

Results of the stability studies should be presented in an appropriate format (e.g., tabular, graphical, narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be indicated.

The actual stability results/reports used to support the proposed shelf-life should be provided in the PD. 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. Dissolution results should be expressed, at minimum, as both the average and range of individual results.

3.2.A Appendices

3.2.A.1 Facilities and Equipment

Not applicable except for biotech products.

3.2.A.2 Adventitious Agents Safety Evaluation

Provide details of any viral safety evaluation and biotech products.

3.2.A.3 Novel Excipients

Provide details of safety (refer to Module 4) and clinical documentation (refer to Module 5) for excipients used for the first time and not used in similar products.

3.2.R Regional Information

3.2.R.1 Production Documentation

3.2.R.1.1 Executed production documents

A minimum of two batches of at least pilot-scale, or in the case of an uncomplicated FPP (e.g., immediate-release solid FPPs (with noted exceptions), non-sterile solutions), not less than one batch of at least pilot-scale (the batch used in comparative bioavailability or biowaiver studies) and a second batch which may be smaller (e.g., for solid oral dosage forms, 25,000 or 50,000 tablets or capsules), should be manufactured for each strength at the time of submission. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch. For solid oral dosage forms, pilot-scale is generally, at a minimum, one-tenth that of full production-scale or 100,000 tablets or capsules, whichever is larger.

Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver or clinical studies. Any notations made by operators on the executed production documents should be clearly legible. If not included in the executed batch records through sufficient in-process testing, data should be provided for the batch used in comparative bioavailability, clinical study, or biowaiver studies that demonstrates the uniformity of this batch. The data to establish the uniformity of the bio batch should involve testing to an extent greater than that required in routine quality control.
English translations of executed records should be provided, where relevant.

3.2.R.1.2 Master production documents

Copies of the FPP master production documents (blank batch manufacturing document) should be provided for each proposed strength, commercial batch size, and manufacturing site. The details in the master production documents should include, but not be limited to, the following:

a) master formula;
b) dispensing, processing, and packaging sections with relevant material and operational details;
c) relevant calculations (e.g., if the amount of API is adjusted based on the assay results or on the anhydrous basis);
d) identification of all equipment by, at minimum, type and working capacity (including make, model, and equipment number, where possible);
e) process parameters (e.g., mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point, tablet machine speed (expressed as target and range));
f) list of in-process tests (e.g., appearance, pH, assay, blend uniformity, viscosity, particle size distribution, LOD, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity, filter integrity checks) and specifications;
g) sampling plan with regard to the:
    - steps where sampling should be done (e.g., drying, lubrication, compression),
    - number of samples that should be tested (e.g., for blend uniformity testing of low dose FPPs, blend drawn using a sampling thief from x positions in the blender), and,
    - frequency of testing (e.g., weight variation every x minutes during compression or

capsule filling);

h) precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times);
i) for sterile products, reference to standard operating procedures (SOP) in appropriate sections and a list of all relevant SOPs at the end of the document;

j) theoretical and actual yield; and,
k) compliance statement with the GMP requirements (refer to documents in Module 1).

[Reference: WHO Technical Report Series, Nos. 902 and No. 908]

3.2.R.2 Analytical Procedures and Validation Information

The tables presented in section 2.3.R.2 in the DOS-PD template should be used to summarize the analytical procedures and validation information from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4 (c), 2.3.S.7.3 (b), 3.2.P.5.2 and 3.2.P.5.3, where relevant.

MODULE 4: NON-CLINICAL STUDY REPORTS

This section of the Guideline is not required for generic products

4.1 Table of Contents of Module 4

A Table of Contents should be provided that lists all of the nonclinical study reports and gives the location of each study report in the PD.

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology
4.2.1.1 Primary Pharmacodynamics
4.2.1.2 Secondary Pharmacodynamics
4.2.1.3 Safety Pharmacology
4.2.1.4 Pharmacodynamic Drug Interactions
4.2.2 Pharmacokinetics
4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)
4.2.2.2 Absorption
4.2.2.3 Distribution
4.2.2.4 Metabolism
4 2.2.5 Excretion
4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
4.2.2.7 Other Pharmacokinetic Studies
4.2.3 Toxicology
4.2.3.1 Single-Dose Toxicity (in order by species, by route)
4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxic kinetics evaluations)
4.2.3.3 Geno toxicity
4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (including supportive toxicokinetic evaluations)
4.2.3.4 Carcinogenicity (including supportive toxicokinetic evaluations)
4.2.3.4.1 Long-term studies (in order by species, including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
4.2.3.4.3 Other studies
4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetic evaluations) [If modified study designs are used, the following sub-headings should be modified accordingly.]
4.2.3.5.1 Fertility and early embryonic development
4.2.3.5.2 Embryo-fetal development
4.2.3.5.3 Prenatal and postnatal development, including maternal function
4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated
4.2.3.6 Local Tolerance
4.2.3.7 Other Toxicity Studies (if available)
4.2.3.7.1 Antigenicity
4.2.3.7.2 Immunotoxicity
4.2.3.7.3 Mechanistic studies (if not included elsewhere)
4.2.3.7.4 Dependence
4.2.3.7.5 Metabolites
4.2.3.7.6 Impurities
4.2.3.7.7 Other
4.3 Literature References

MODULE 5: CLINICAL STUDY REPORTS

This section of the Guideline is applicable only for medicines where a BE study is a requirement and where the medicine is not yet registered in Liberia. For FPPs in which the molecule(s) is new to the Liberian market, the applicant should submit full safety and efficacy data as outline in this Guideline. For multisource generic products having a molecule(s) already registered in Liberia and requiring BE study, only section 5.3.3 of Module 5 needs to be supported with actual experimental evidence and where applicable reference to literature can be considered for other section. For generic products requiring clinical equivalence study, in cases where comparative clinical evidence of a pharmacokinetics (PK) BE study cannot be conducted, section 5.3.4 of Module 5 may be required, to be determined on a case-by-case basis.

The information provided below is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that need to be submitted with the application.

The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation, such as —not applicable‖ or —no study conducted, should be provided when no report or information is available for a section or subsection.

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

A tabular listing of all clinical studies and related information should be provided. For each study, this tabular listing should generally include the type of information identified in Table 5.1 of this Guideline. Other information can be included in this table if the applicant considers it useful. The sequence in which the studies are listed should follow the sequence described in Section 5.3 below. Use of a different sequence should be noted and explained in an introduction to the tabular listing.

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

BA studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or BE studies may use PK, PD, clinical, or in vitro dissolution endpoints, and may be either single dose or multiple dose. When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.

5.3.1.1 Bioavailability (BA) study reports

BA studies in this section should include: Guideline for Registration of Medicines

- studies comparing the release and systemic availability of a drug substance from a solid oral dosage form to the systemic availability of the drug substance given intravenously or as an oral liquid dosage form;
- dosage form proportionality studies; and,
- food-effect studies.

Reference to literature suffices for generic products.

5.3.1.2 Comparative BA and BE study reports

Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g., tablet to tablet, tablet to capsule). Comparative BA or BE studies may include comparisons between

- the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product, the drug product used in clinical studies supporting effectiveness, and the drug product used in stability batches; and,
- similar drug products from different manufacturers.

5.3.1.3 In vitro–in vivo correlation study reports

In vitro dissolution studies that provide BA information, including studies used in seeking to correlate in vitro data with in vivo correlations, should be placed in section 5.3.1.3. Reports of in vitro dissolution tests used for batch quality control and/or batch release should be placed in the Quality section (module 3) of the pd.

5.3.1.4 Reports of bioanalytical and analytical methods for human studies

Bioanalytical and/or analytical methods for biopharmaceutic studies or in vitro dissolution studies should ordinarily be provided in individual study reports. Where a method is used in multiple studies, the method and its validation should be included once in section 5.3.1.4 and referenced in the appropriate individual study reports.

5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues, and related materials derived from human sources that are used in vitro or ex vivo to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes, and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Module 4).

5.3.2.1 Plasma protein binding study reports

Ex vivo protein binding study reports should be provided here. Protein binding data from PK blood and/or plasma studies should be provided in section 5.3.3.

5.3.2.2 Reports of hepatic metabolism and drug interaction studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

5.3.2.3 Reports of studies using other human biomaterials

Reports of studies with other biomaterials should be placed in this section.

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolite(s), in particular, those that have pharmacological activity. The PK studies whose reports should be included in sections 5.3.3.1 and 5.3.3.2 are generally designed to: (1) measure plasma drug and metabolite concentrations over time; (2) measure drug and metabolite concentrations in urine or feces, when useful or necessary; and/or, (3) measure drug and metabolite binding to protein or red blood cells. On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in section 5.3.3.1 to 5.3.3.2, as appropriate. These studies should characterize the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of a drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be included in sections 5.3.3.1 and/or 5.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. The study of human PK study reports should fulfill the requirements for bioequivalence as described in this Guideline.

5.3.3.1 Healthy subject PK and initial tolerability study reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this section.

5.3.3.2 Patient PK and initial tolerability study reports

Reports of PK and initial tolerability studies in patients should be placed in this section. Most of the time for generic products, cross-reference to literature suffices. However, when PK studies are not possible on healthy subjects because of toxicity and other issues, this section should be completed where applicable.

5.3.3.3 Intrinsic factor PK study reports

Reports of PK studies to assess effects of intrinsic factors, should be placed in this section. Reports of PK studies to assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) factors should be placed in this section.

5.3.3.4 Extrinsic factor PK study reports

Reports of PK studies to assess effects of extrinsic factors (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors should be organized in this section.

5.3.3.5 Population PK study reports

Reports of population PK studies based on sparse samples obtained in clinical trials, including efficacy and safety trials, should be placed in this section.

5.3.4 Reports of Human Pharmacodynamic (PhD) Studies

This section of the Guideline does not require experimental evidence for generic products and medicines already registered in Liberia. Exceptions are when meaningful PK studies cannot be conducted as a result of difficulties, such as inadequate measurement of the active pharmaceutical substance in biological fluids. Report should be presented in this section for further clarification.

Reports of studies with a primary objective of determining the PhD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data, however, should be placed in section 5.3.5. This section should include reports of: (1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers); (2) short-term studies of the main clinical effect; and, (3) PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose response studies or together with drug concentration information in PK studies (concentration-response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an

appropriate model and used as a basis for designing further dose-response studies or, in some cases, for interpreting effects of concentration differences in population subsets.
Dose-finding, PD, and/or PK-PD studies can be conducted in healthy subjects and/or patients, and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD, and/or PK/PD studies conducted in healthy subjects should be placed in section 5.3.4.1, and the reports for those studies conducted in patients should be placed in section 5.3.4.2.

In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy, either because they show an effect on an acceptable surrogate marker (e.g., blood pressure) or on a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study may contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in section 5.3.5, not in section 5.3.4.

5.3.4.1 Healthy subject PD and PK/PD study reports

PD and/or PK/PD studies having non-therapeutic objectives in healthy subjects should be placed in this section.

5.3.4.2 Patient PD and PK/PD study reports

PD and/or PK/PD studies in patients should be submitted in this section.

5.3.5 Reports of Efficacy and Safety Studies

For generic medicines in which the molecule(s) of FPP are registered in Ethiopia cross reference to literature will suffice. This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor, or otherwise available, including all completed and all ongoing studies of the drug in proposed and non-proposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate section 5.3.5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, it should be included in the appropriate section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate section 5.3.5 and referenced as necessary in other sections 5.3.5, for example, section 5.3.5A, section 5.3.5B.

5.3.5.1 Study reports of controlled clinical studies pertinent to the claimed indication

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses);
- No-treatment control;
- Dose-response (without placebo);
- Active control (without placebo); or,
- External (historical) control, regardless of the control treatment.

Within each control type, where relevant to the assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in section 5.3.5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in section 5.3.5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in section 5.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in section 5.3.5.1.

5.3.5.2 Study reports of uncontrolled clinical studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in section 5.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

5.3.5.3 Reports of analyses of data from more than one study

Examples of reports that would be found in this section include: a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations, and a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.

5.3.5.4 Other study reports

- Reports of interim analyses of studies pertinent to the claimed indications;
- Reports of controlled safety studies not reported elsewhere; and,
- Reports of controlled or uncontrolled studies not related to the claimed indication

5.3.6 Reports of Post-Marketing Experience

For products that are currently marketed, reports that summarize marketing experience (including all significant safety observations) should be included in this section.

5.3.7 Case Report Forms and Individual Patient Listings

Case report forms and individual patient data listings are subject to good clinical practice inspection where applicable.

5.4 Literature References

Copies of referenced documents, including important published articles, official meeting minutes, or other regulatory guidance or advice should be provided here. This includes: copies of all references cited in the Clinical Overview, and copies of important references cited in the Clinical Summary or in the individual technical reports that were provided in Module 5. Only one copy of each reference should be provided. Copies of references that are not included here should be immediately available upon request.

MODULE 2.3: QUALITY OVERALL SUMMARY: PRODUCT DOSSIER (QOS-PD)

See sections 1.5, 3 and 4 of "Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part" for general and detailed instructions on the completion of this template.

INTRODUCTION

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	
Reference Number(s)	
Strength(s)	
Route of administration	
Proposed indication(s)	
Contact person responsible for this application	Title: Name: Phone: Fax: Email:

If there are other contacts who should be routinely copied into correspondence for this application, they should also be listed below.

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

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

Name of API:	
Name of API manufacturer:	
□	Confirmation of API Prequalification document: • a copy of the confirmation of API Prequalification document should be provided in *Module 1*, and • summaries of the relevant information should be provided under the appropriate sections (e.g. S.1.3, S.2, S.3.1, S.4.1 through S.4.4, S.5 and S.7; see Quality guideline).
□	Certificate of suitability to the European Pharmacopoeia (CEP): • is a written commitment provided that the applicant will inform WHO in the event that the CEP is withdrawn and acknowledged that withdrawal of the CEP will require additional consideration of the API data requirements to support the dossier: □ yes, □ 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 FPP manufacturer or applicant to PQTm who refers to the CEP; and • summaries of the relevant information should be provided under the appropriate sections (e.g. S.1.3, S.3.1, S.4.1 through S.4.4, S.5, S.6 and S.7; see Quality guideline).
□	Active pharmaceutical ingredient master file (APIMF): • a copy of the letter of access should be provided in *Module 1*; 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.
□	Active pharmaceutical ingredient pre-qualified by WHO Provide evidence from WHO
□	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 (name, manufacturer)

2.3.S.1.1 Nomenclature (name, manufacturer)

(a) **(**Recommended) International Non-proprietary name (INN):
(b) Compendia 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 (name, manufacturer)

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

2.3.S.1.3 General Properties (name, manufacturer)

(a) Physical description (e.g. appearance, color, physical state):
(b) Solubility:

In common solvents:
Quantitative aqueous pH solubility profile (pH 1.2 to 6.8) at 37°C:

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

Dose/solubility volume calculation:

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

Polymorphic form:
Solvate:
Hydrate:

(d) **Other:**

Property	
pH	
pK	
Partition coefficients	
Melting/boiling points	
Specific optical rotation (specify solvent)	
Refractive index (liquids)	
Hygroscopicity	
UV absorption maxima/molar absorptivity	
Other	

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.2.1 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**	**API-PQ number/APIMF/CEP number (if applicable)**

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

2.3.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)

(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 Materials (name, manufacturer)

(a) Name of starting material:
(c) Name and manufacturing site address of starting material manufacturer(s):
(d) Summary of the quality and controls of the starting materials used in the manufacture of the API:

Step / Starting Material	**Test(s)/method(s)**	**Acceptance criteria**

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

2.3.S.2.4 Controls of Critical Steps and Intermediates (name, manufacturer)

(a) 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 Evaluation (name, manufacturer)

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

2.3.S.2.6 Manufacturing Process Development (name, manufacturer)

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

2.3.S.3 Characterization (name, manufacturer)

2.3.S.3.1 Elucidation of Structure and other Characteristics (name, manufacturer)

(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 centers and configurations) of the API batch(es) used in comparative bioavailability or bio-waiver studies:

(c) Summary of studies performed to identify potential polymorphic forms (including solvates): <including identification of and data on the API lot used in bioavailability studies>

(d) Summary of studies performed to identify the particle size distribution of the API: <including identification of and data on the API lot used in bioavailability studies>

(e) Other characteristics:

2.3.S.3.2 Impurities (name, manufacturer)

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

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

API-related impurity (chemical name and 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 API administered per day) for the API, corresponding to ICH Reporting/Identification/Qualification Thresholds for the API-related impurities and the concentration limits (ppm) for the process-related impurities (e.g. residual solvents):

ii.

Maximum daily dose for the API:	**<x mg/day>**	
Test	**Parameter**	**ICH threshold or concentration limit**
API-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 (API-related and process-related)	**Acceptance Criteria**	**Results (include batch number* and use**)**		

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

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

iii. Justification of proposed acceptance criteria for impurities:

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

2.3.S.4.1 Specification (name, manufacturer)

(a) API specifications of the FPP manufacturer:

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

2.3.S.4.2 Analytical Procedures (name, manufacturer)

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

2.3.S.4.3 Validation of Analytical Procedures (name, manufacturer)

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

See *2.3.R Regional Information* for summaries of the validation information (i.e. *2.3.R.2 Analytical Procedures and Validation Information*).

Summarized tabulated methods and validation may be provided in a separate file <provide reference>.

2.3.S.4.4 Batch Analyses (name, manufacturer)

(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 FPP 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 (name, manufacturer)

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

compendia standard(s)):

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

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

(b) Characterization and evaluation of non-official (e.g. not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g. elucidation of structure, certificate of analysis):

(c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard):

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

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

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

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

2.3.S.7 Stability (name, manufacturer)

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

(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 and peak purity are observed)
Heat		
Humidity		
Oxidation		
Photolysis		
Acid		
Base		
Others		

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

Storage condition (◦C, % 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 (limits)	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*

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

2.3.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)

(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>*	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

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

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

2.3.S.7.3 Stability Data (name, manufacturer)

(a) The actual stability results should be provided in *Module 3*.

(b) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4 (e.g. analytical procedures used only for stability studies):

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

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

Component and quality standard (and grade, if applicable)	Function	Strength (label claim)					
		Quant. per unit or per mL	%	Quant. per unit or per mL	%	Quantity per unit or per mL	%
<complete with appropriate title e.g. Film-coating >							
Subtotal 2							
Total							

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

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

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

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the FPP

2.3.P.2.1.1 Active Pharmaceutical Ingredient

(a) Discussion of the:

i. compatibility of the API(s) with excipients listed in 2.3.P.1:

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

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

2.3.P.2.1.2 Excipients

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

2.3.P.2.2 Finished Pharmaceutical Product

2.3.P.2.2.1 Formulation Development

(a) Summary describing the development of the FPP (e.g. route of administration, usage, optimization of the formulation, etc.):

(b) Information on primary (submission, registration, exhibit) batches including comparative bioavailability or bio-waiver, stability, commercial:

i. **Summary of batch numbers:**

Batch number(s) of the FPPs used in			
Bioequivalence or bio-waiver	**<e.g. bioequivalence batch A12345>** **<e.g. bio-waiver batch X12345>**		
For proportional strength bio-waiver: 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) if available			
‹ packaging configuration I›			
‹ packaging configuration II›			
(Add/delete as many rows as necessary)			
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. NF, BP, Ph.Eur, in-house)	Relevant batches							
	Comparative bioavailability or bio-waiver		Stability		Process validation		Commercial (2.3.P.1)	
	<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>	
	Theoretical quantity per batch	%	Theoretical quantity per batch	%	Theoretical quantity per batch	%	Theoretical quantity per batch	**%**
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>								
Subtotal 1								
<complete with appropriate title e.g. Film-coating >								
Subtotal 2								
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 bio-waiver), 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):

Summary of the multi-point dissolution profiles for the bio-batch (es) in three BCS media across the physiological pH range and the proposed medium if different from the BCS media:

(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

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

2.3.P.2.2.3 Physicochemical and Biological Properties

(a) Discussion of the parameters relevant to the performance of the FPP (e.g. pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):

2.3.P.2.3 Manufacturing Process Development

(a) Discussion of the development of the manufacturing process of the FPP (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 bio-waiver 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 FPP (e.g. choice of materials, protection from moisture and light, compatibility of the materials with the FPP):

(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 for the lowest intended dose):

2.3.P.2.5 Microbiological Attributes

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

2.3.P.2.6 Compatibility

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

2.3.P.3 Manufacture

2.3.P.3.1 Manufacturer(s)

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

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

(b) Manufacturing authorization, marketing authorization and, where available, WHO-type certificate of GMP (GMP information should be provided in *Module 1*):

2.3.P.3.2 Batch Formula

Largest intended commercial batch size:
Other intended commercial batch sizes:

<information on all intended commercial batch sizes should be in the QOS-PD>

(a) List of all components of the FPP 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 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			

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:

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:

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

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

2.3.P.3.5 Process Validation and/or Evaluation

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

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

2.3.P.4 Control of Excipients

2.3.P.4.1 Specifications

(a) Summary of the specifications for in-house standard specifications:

2.3.P.4.2 Analytical Procedures

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

2.3.P.4.3 Validation of Analytical Procedures

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

2.3.P.4.4 Justification of Specifications

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

2.3.P.4.5 Excipients of Human or Animal Origin

(a) For FPPs 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 Novel Excipients

Novel excipients are not accepted in scientific discussion (PQTm). See quality guideline for definition.

2.3.P.5 Control of FPP

2.3.P.5.1 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.			

2.3.P.5.2 Analytical Procedures

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

2.3.P.5.3 Validation of Analytical Procedures

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

2.3.P.5.4 Batch Analyses

(a) Description of the batches:

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

(b) Summary of batch analyses release results for relevant batches (e.g. comparative bioavailability or bio-waiver, 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.5.2 and 2.3.P.5.3 (e.g. historical analytical procedures):

2.3.P.5.5 Characterization of Impurities

(a) Identification of potential and actual impurities:

Degradation product (code name, chemical name and compendia name (e.g. USP RC A) if relevant)	**Structure**	**Origin**

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

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

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

Maximum daily dose for the API:	**<x mg/day>**	
Test	**Parameter**	**ICH 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 bio-waiver):

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

iii. Justification of proposed acceptance criteria for impurities:

2.3.P.5.6 Justification of Specification(s)

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

2.3.P.6 Reference Standards or Materials

(a) Source (including lot number) of primary reference standards or reference materials (e.g. Ph.Int., Ph.Eur., BP, USP, in-house) *not* discussed in 3.2.S.5:

(b) Characterization and evaluation of non-official (e.g. not from an officially recognized pharmacopoeia) primary reference standards or reference materials (e.g. elucidation of structure, certificate of analysis) *not* discussed in 3.2.S.5:

(c) Description of the process controls of the secondary reference standard (comparative certificate of analysis and IR spectra against primary standard) *not* discussed in 3.2.S.5:

2.3.P.7 Container Closure System

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

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

(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.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

(a) Summary of stress testing and results (e.g. photostability studies, cyclic studies, freeze-thaw studies, demonstration of stability-indication of purity/assay method(s)):

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

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

Summary of additional stability studies, if applicable (with reference to data location) *<e.g. studies at intermediate conditions, holding period studies for intermediates and bulk product, transport studies, in-use studies>:*

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

Container closure system	Storage statement	Shelf-life

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

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

Parameter	Details	
Storage condition(s) (◦C, % RH)		
Batch number(s) / batch size(s)	*<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	
	etc.	
Testing frequency		
Container closure system(s)		

2.3.P.8.3 Stability Data

(a) The actual stability results should be provided in *Module 3*.

(b) Summary of analytical procedures and validation information for those procedures *not* previously summarized in 2.3.P.5 (e.g. analytical procedures used only for stability studies):

(c) Bracketing and matrixing design and justification for *Commitment* and/or *Ongoing stability batches*, if applicable:

2.3.A APPENDICES

2.3.A.1 Facilities and Equipment (name, manufacturer)

(a) Summary of information on facilities and equipment, in addition to the information provided in other sections of the submission: If applicable.

2.3.A.2 Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)

(a) Summary of the information assessing the risk with respect to potential contamination with adventitious agents: If applicable.

2.3.A.3 Excipients

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

2.3.R REGIONAL INFORMATION

2.3.R.1 Production Documentation

2.3.R.1.1 Executed Production Documents

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

2.3.R.1.2 Master Production Documents

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

2.3.R.2 Analytical Procedures and Validation Information

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES			
ATTACHMENT NUMBER:			
HPLC Method Summary		**Volume/Page:**	
Method name:			
Method code:		**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 preparation and concentration (expressed as mg/ml, let this be termed “A”):			
Reference solution preparation and concentration (expressed as mg/ml and as % of “A”):			
System suitability solution concentration (expressed as mg/ml and as % of “A”):			
System suitability tests (tests and acceptance criteria):			
Method of quantification (e.g. against API or impurity reference standard(s)):			
Other information (specify):			

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

QUALITY INFORMATION SUMMARY (QIS)

INTRODUCTION

(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			
Reference Number(s)			
Strength(s)			
Route of administration			
Proposed indication(s)			
Primary contact person responsible for this application[1]	Title: First name: Family Name:		
Contact person's job title			
Contact person's postal address			
Unit			
Building/PO Box number			
Road/Street			
Plant/Zone			
Village/suburb			
Town/City			
District and Mandal			
Province/State			
Postal code			
Country			
Contact person's email address			
Contact person's phone number			

1 *Please note that the contact listed in this form will be the primary contact for email and mail communication for this specific application.*

(b) Administrative Summary:

Applicant's date of preparation or revision of the QIS	
Internal version and/or date of acceptance	*(WHO use only)*

Related dossiers (e.g. FPP(s) with the same API(s) submitted to the Prequalification Team: medicines (PQTm) by the applicant):

Reference number (e.g. HA998)	**Prequalified (Y/N)**	**API, strength, dosage form (eg. Abacavir (as sulphate) 300 mg tablets)**	**API manufacturer (including address if same supplier as current dossier)**

2.3.S 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:	
□	Confirmation of API prequalification document
□	Certificate of suitability to the European Pharmacopoeia (CEP)
□	Active pharmaceutical ingredient master file (APIMF) procedure: APIMF number assigned by WHO (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: : _____.
□	Full details in the PD Document version number/identifier of current module 3.2.S: _____

2.3.S.2 Manufacture (name, manufacturer)

2.3.S.2.1 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	API-PQ number /APIMF/CEP number (if applicable)	Letter of access provided?

2.3.S.2.3 Control of Materials (name, manufacturer) – for API option 4 only

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

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

2.3.S.4.1 Specification (name, manufacturer)

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

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

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

(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)

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

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

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

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

2.3.P.2.2.1 Formulation Development

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

(i) Summary of batch numbers:

PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION

BIOEQUIVALENCE TRIAL INFORMATION

1 SUMMARY

1.1 Summary of bioequivalence studies performed

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

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

(State the location of the master formulae in the quality part of the submission) (Tabulate the composition of the biobatch using the table below. For solid oral dosage forms the table should contain only the ingredients in tablet core /contents of a capsule. A copy of the table should be filled in for the film coating / hard capsule, if any. ***Important****: If the formulation proposed for marketing and those used for bioequivalence studies are not identical, copies of this table should be filled in for each formulation with clear identification in which bioequivalence study the respective formulation was used.)*

Composition of the batches used for bioequivalence studies					
Batch number					
Batch size (number of unit doses)[2]					
Comments, if any					
Comparison of unit dose compositions and of clinical FPP batches (duplicate this table for each strength, if compositions are different)					
Ingredients (and quality standard)	Function	Unit dose (mg)	Unit dose (%)	Biobatch (kg)	Biobatch (%)
Total					
Equivalence of the compositions or justified differences					
Maximum intended commercial batch size					

2 CLINICAL STUDY REPORT

a) Study number:
b) Study title:
c) Location of study protocol:
d) Start and stop dates for each phase of the clinical study:
e) Dates of product administration:

2.1 ETHICS

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

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

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

2.2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

a) Name of principal investigator(s) *(State location of c.v. in the submission)*

b) Clinical Facility *(Name and full mailing address)*

c) Clinical Laboratories *(Name and full mailing address)*

d) Analytical Laboratories *(Name and full mailing address)*

e) Company performing pharmacokinetic/statistical analysis *(Name and full mailing address)*

2.3 STUDY OBJECTIVES

Briefly state the study objectives.

2.4 INVESTIGATIONAL PLAN

2.4.1 Overall study design and plan — description

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

2.4.2 Selection of study population

2.4.2.1 Inclusion Criteria

(List the inclusion criteria applied to subjects)

2.4.2.2 Exclusion Criteria

(List the exclusion criteria applied to subjects)

2.4.2.3 Health Verification

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

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

b) Indicate when tests were performed

c) <u>Study site normal values</u>
(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)

d) Report any results that were outside of study site normal values
(State location in submission of the summary of anomalous values)

2.4.2.4 Removal of Trial subjects from Trial or Assessment

a) Number of subjects enrolled in the study
(All subjects including alternates, withdrawals, and dropouts)

b) Alternates
(Please note: Generally all subjects enrolled in the study should be included in the data set i.e., alternate subjects are strongly discouraged. However, in cases where there are alternate subjects, describe the procedure of including/excluding the alternates and whether alternates have been included in the study)

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

2.4.3 Products Administered

2.4.3.1 Test Product

a) Batch number, size, date of manufacture and expiry date for the test product

b) Potency (measured content) of test product as a percentage of label claim as per validated assay method
(This information should be cross-referenced to the location of the certificate of analysis in the submission)

2.4.3.2 Comparator (Reference) Product

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

a) Name and manufacturer of the comparator product and market where the comparator product was purchased

b) Batch number and expiry date for the comparator product

c) Purchase, shipment, storage of the comparator product
(Indicate from which company/pharmaceutical distributor the comparator product has been obtained. Clearly indicate in chronological order the steps and dates of shipment/transport from company of purchase to the study site. In addition, the storage conditions should be given. This information should be cross-referenced to location in submission of documents (e.g. receipts) proving conditions)

d) Potency (measured content) of the comparator product as a percentage of label claim, as measured by the same laboratory and under the same conditions as the test product
(This information should be cross-referenced to the location of the certificate of analysis in the submission)

e) Justification of choice of comparator product
(Provide short summary here and cross-reference to location of comprehensive justification in study protocol)

2.4.4 Selection of doses in the study

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

2.4.5 Selection and Timing of Dose for Each Subject

a) State volume and type of fluid consumed with dose

b) Interval between doses *(i.e., length of washout)*

c) Protocol for the administration of food and fluid

d) Restrictions on posture and physical activity during the study

2.4.6 Blinding

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

a) study monitors: Yes ☐ / No ☐ If No, justify:
b) subjects: Yes ☐ / No ☐ If No, justify:
c) analysts: Yes ☐ / No ☐ If No, justify:

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

2.4.7 Drug Concentration Measurements

2.4.7.1 Biological fluid(s) sampled

2.4.7.2 Sampling protocol

a) Number of samples collected per subject
b) Volume of fluid collected per sample
c) Total volume of fluid collected per subject per phase of the study
d) List the study sampling times

e) Identify any deviations from the sampling protocol
(State location of summary in the submission)
(Describe and explain reasons for deviations from sampling protocol. Comment on impact on study. Indicate whether the deviations were accounted for in the pharmacokinetic analysis)

2.4.7.3 Sample Handling

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

Comment from Assessors

3 TRIAL SUBJECTS

3.1 Demographic and other baseline characteristics

a) Identify study population (i.e., normal, healthy adult volunteers or patients)
b) Summary of ethnic origin and gender of subjects
c) Identify subjects noted to have special characteristics and state notable characteristics *(e.g. fast acetylators of debrisoquine)*
d) Range and mean age ± SD of subjects
e) Range and mean height and weight ± SD of subjects
f) Identify subjects whose ratio is not within 15% of the values given on a standard height/weight table

3.2 Subjects who smoke

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

3.3 Comments from review of Section 3 – Assessors use only

4 PROTOCOL DEVIATIONS

4.1 Protocol deviations during the clinical study

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

4.2 Comments from review of Section 4 – Assessors use only

5 SAFETY EVALUATION

5.1 Identify adverse events observed

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

5.2 Comments from review of Section 5 – Assessors use only

6 EFFICACY EVALUATION

Efficacy results and tabulations of individual trial subject's data

6.1 Presentation of data

a) State location in submission of tables of mean and individual subject concentrations

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

6.2 Pharmacokinetic (PK) parameters

a) State how the pharmacokinetic parameters where calculated/obtained for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, C_{max}, tmax, the elimination rate constant, and $t_{½}$ (indicate location of description in protocol)

b) State whether actual sampling time points were used for estimation of the pharmacokinetic parameters

c) Complete the table below

	Test			Reference		
Parameter	Arithmetic mean	Standard deviation	Interindividual coefficient of variation (%)	Arithmetic mean	Standard deviation	Interindividual coefficient of variation (%)
AUC0-t (units)						
AUC0-inf (units)						
Cmax (units)						
tmax (units)						
t½ (units)						

d) Ratio of AUC_{0-t} to AUC_{0-inf}

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

6.3 Statistical analysis

(State the method of calculation of the 90% confidence intervals for the ratio of test formulation over the reference formulation and indicate how treatment, period, sequence and subjects within sequence were included as factors in the ANOVA. Provide the following results from the ANOVA (parametric) on the logarithmically transformed AUC_{0-t} and C_{MAX} and other relevant parameters. State software used for computing ANOVA.)

a) Geometric means, results from ANOVA, Degrees of Freedom (DF) and derived CV (intra-subject)

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)						
AUC0-inf (units)						
Cmax (units)						

b) Comparison of the results

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

6.4 Discussion of results

(State location of the discussion of the results in the submission)

6.5 Comments from review of Section 6 – Assessors use only

7 ANALYTICAL VALIDATION REPORT

7.1 ***Analytical*** technique

7.1.1 Validation protocol

(State the location of the validation protocol)

7.1.2 Identify analyte(s) monitored

7.1.3 Comment on source and validity of reference standard

7.1.4 Identify internal standard

7.1.5 Comment on source and validity of internal standard

7.1.6 Identify method of extraction

7.1.7 Identify analytical technique or method of separation employed

7.1.8 Identify method of detection

7.1.9 Identify anticoagulant used *(if applicable)*

7.1.10 If based on a published procedure, state reference citation

7.1.11 Identify any deviations from protocol

7.2 Selectivity

(Address the methods to verify selectivity against endogenous/exogenous compounds & results)

7.3 Sensitivity

(Address the methods to verify sensitivity & results)

7.4 Carry-over

(Summarize the method to verify carry-over & results)

7.5 Standard curves

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

a) List number and concentration of calibration standards used

b) Describe the regression model used including any weighting

c) List the back-calculated concentrations of the calibration standards of the validation runs *(highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)*

7.6 Quality control samples

a) Identify the concentrations of the QC samples and the storage conditions employed prior to their analysis

7.7 Precision and accuracy during validation

a) Summarize inter-day/inter-run accuracy and precision of the calibration standards during assay validation

b) Summarize inter-day/inter-run accuracy and precision of the calibration standards during assay re-validation
(If applicable)

c) Summarize inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay validation

d) Summarize inter-day/inter-run and intra-day/intra-run accuracy and precision of the QC samples during assay re-validation
(If applicable)

7.8 Dilution integrity

(Summarize the method to verify dilution integrity & results)

7.9 Matrix effect (in case of MS detection)

(Summarize methods to verify the matrix effect & results)

7.10 Stability

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

a) Summarize data on long-term storage stability
b) Summarize data on freeze-thaw stability
c) Summarize data on bench top stability
d) Summarize data on auto-sampler storage stability
(e) Summarize data from any other stability studies conducted
(e.g. long-term stock solution and working solution stability, short-term stock solution and working solution stability, dry-extract stability, wet-extract stability, stability in blood before sample processing)

7.11 Re-injection reproducibility

(Summarize the method to verify re-injection reproducibility & results)

7.12 Comments from review of Section 7 – Assessors use only

8 BIOANALYTICAL STUDY REPORT

(State the location of the bioanalytical report for the analysis of the study subject samples)

8.1 Analytical technique

(Confirm whether the method is the same as the validated method and whether the same equipment was employed. Identify any differences between the validated method described above in Section 7 and the method employed for subject sample analyses)

8.1.1 Analytical protocol

(State the location of the analytical protocol)

8.1.2 Identify any deviations from protocol

8.1.3 Dates of subject sample analysis

8.1.4 Longest period of subject sample storage

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

8.1.5 State whether all samples for a given subject were analyzed together in a single analysis run

8.2 Standard curves

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

a) List number and concentration of calibration standards used

b) State number of curves run during the study *(valid and failed runs, including reasons of failure)*.

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

d) List the back-calculated concentrations of the calibration standards of the study runs *(highlight the values outside of the acceptance range, e.g., 15%, except 20% for LLOQ)*

8.3 Quality control samples

a) Identify the concentrations of the QC samples, their date of preparation and the storage conditions employed prior to their analysis

b) State the number of QC samples in each analytical run per concentration

c) List the back-calculated concentrations of the QC samples of the study runs *(highlight the values outside of the acceptance range, e.g., 15%)*

d) Discuss whether the concentrations of the QC sample concentrations are similar to the concentrations observed in the study samples

e) State the percentage of QC samples per run with respect to the total number samples assayed in each run

8.4 Precision and accuracy

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

8.5 Repeat analysis (re-analysis, re-injection and re-integration)

a) List re-analysed samples by sample identification and include the following information for each re-analysis: initial value; reason for re-analysis; re-analysed value(s); accepted value; and reason for acceptance

b) Report the number of re-analysis as a percentage of the total number samples assayed

c) List re-injected samples by sample identification and include the following information for each re-injection: initial value; reason for re-injection; re-injected value; accepted value; and reason for acceptance

d) Report the number of re-injections as a percentage of the total number samples assayed

e) List re-integrated chromatograms by sample identification and include the following information for each re-integration: initial value; reason for re-integration; re-integrated value(s); accepted value; and reason for acceptance

f) Report the number of re-integrated chromatograms as a percentage of the total number of samples assayed

8.6 Incurred sample reanalysis

(State location in the submission and summarize the results of incurred sample reanalysis, including the number of subject samples included in ISR and the total number of samples analysed in the study)

8.7 Chromatograms

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

8.8 Comments from review of Section 9 – Assessors use only

9 QUALITY ASSURANCE

9.1 Internal quality assurance methods

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

9.2 Monitoring, auditing, inspections

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

9.3 Comments from review of Section 10 – Assessors use only

10.0 CONCLUSIONS AND RECOMMENDATIONS – Assessors use only

ANNEX B1- MODEL COVER LETER

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

<Applicant's reference> <Date>

Liberia Medicines and Health Products Regulatory Authority
2nd & 3rd Floors Clay Building, Sekou Toure Avenue, Mamba Point, Monrovia, Liberia

Dear Sir:

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

We are pleased to submit our Application Dossier(s) for the registration of human medicines in *Liberia* for the following product(s):

Name of the medicinal product(s): ……..……..
Pharmaceutical form(s) and strength(s): ……..
INN/active Pharmaceutical ingredient(s): …….....
ATC Code(s): ……..……..

<The application seeks market authorization for a new product not previously marketed in the ECOWAS or any member country.>

<The application seeks to renew the following marketing authorization(s) …..>

<The application seeks a market authorization for a variation of <indicate the product and market authorization # or previous application identifiers, e.g., LMHRA Registration numbers>>

<This submission responds to correspondence from <name of regulatory authority, (e.g., ECOWAS or member country), dated <DAY, MONTH, YEAR>, related to application number <#####>. The regulator's correspondence is provided in module 1.1.2. The response to the correspondence is provided in module 1.1.3.>

You will find enclosed the submission dossier as specified hereafter:

☐ CTD format, 2 copies (following the regulator requirements):

- ☐ Soft copy
- ☐ Hard copy
- ☐ Both

☐ CD ROM; Summaries in word format and body data in PDF format

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

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

☐ The electronic submission contains the following modules*:*
<- Module 1: Administrative information and product information
- Module 2: Overview and summaries

- *Module 3: Quality*
- *Module 4: Non clinical study reports*
- *Module 5: Clinical study reports>*

<*The relevant fees have been paid.>*

<*xxx samples of the drug product have been submitted with this application.>*

Yours sincerely,

……
<Signature>
<Name>
<Title>
<Phone number(s)>
<Email address>

ANNEX B_2 MODEL LETTER OF ACCESS TO CEP

Include the letter in Module 1 – Administration and Product Information, sub module 1.2.6 of the application in CTD format

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

<Applicant's reference> <Date>

Liberia Medicines and Health Products Regulatory Authority
2nd & 3rd Floors, Clay Building, Sekou Toure Avenue, Mamba Point, Monrovia, Liberia

Dear Sir:

Subject: Authorization to access Certificate of Suitability (CEP)

Reference is made to the above subject matter.

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

This consent <*includes / 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 the <*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 WAHO 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 *Liberia an ECOWAS member country* before written approval is granted by the Liberia Medicines and Health Products Regulatory Authority.

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

Any questions arising from the Liberia Medicines and Health Products Regulatory Authority.
evaluation of this CEP should be forwarded to:
(*Name and address*)

Yours faithfully

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