



# REGISTRATION OF PHARMACEUTICAL PRODUCTS FOR HUMAN USE IN THE ECONOMIC COMMUNITY OF WEST AFRICAN STATES

Guidance for the Preparation of Applications in the  
Common Technical Document (CTD) Format



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June 2018

## FOREWORD

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 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.

ECOWAS, in recognizing that all the fifteen member states have different requirements for submission of their dossiers for the granting of marketing authorization, initiated interventions and activities to harmonize medical product registration as part of overall process of harmonizing drug regulations in the region.

This initiative resulted in the development of registration requirements based on CTD format that were validated, and adopted by member states in 2010. Subsequent to that a number of countries including Nigeria, Ghana, Liberia, Sierra Leone and The Gambia have largely adopted the CTD format into their processes of granting of marketing authorization.

In the process the eight WAEMU member states within the region had also developed a set of CTDs that are being used in some of the countries<sup>1</sup>.

The effect is that industry will have to contend with two different set of requirements in CTD formats in the ECOWAS region that may lead to delays in the registration of critical products for public health interventions, such as those for HIV/AIDS, Malaria, Tuberculosis, the recent Ebola outbreak and other neglected tropical diseases, leading to limited access to these medicines by the people who need them most.

It has become imperative that in order to improve access and to facilitate the interventions that are supported by development partners and governments in the region, these two documents for medicines registration are reviewed, harmonized in line with international standards, approved and implemented by member states as part of the overall harmonization of medicine regulation.

Based on the experience of WHO in providing technical assistance to various regions for the development and harmonization of medicines registration, ECOWAS requested WHO to review the two documents existing in the region and align them into a single registration document based of the CTD format.

Medicines Regulatory staff will be trained in the harmonized requirements in CTD format and processes to facilitate their use at country level. The same requirements will be used when the need arises to register some medicines at the regional level under the auspices of WAHO.

It is believed that the use of the CTD by all NMRAs in the 15 member states will facilitate easy submissions, reduce cost of both submission and assessment, improve collaboration and information exchange between regulators, reduce registration life cycles and ultimately improve access to critical and essential medicines in the region.

Prof. Stanley OKOLO  
Director -General

<sup>1</sup> Regulation No. 06/2010 / CM / 2010 / UEMOA on the Procedures for the Registration of Pharmaceutical Products for Human Use in UEMOA Member States.

## PREFACE

Established on May 28 1975 via the treaty of Lagos, the Economic Community of West African States (ECOWAS) is a 15-member regional group with a mandate of promoting economic integration in all fields of activity of the constituting countries. Member countries making up ECOWAS are Benin, Burkina Faso, Cape Verde, Cote d' Ivoire, The Gambia, Ghana, Guinea, Guinea Bissau, Liberia, Mali, Niger, Nigeria, Sierra Leone, Senegal and Togo.

The West African Health Organization (WAHO) was formed in 1987 when the Heads of State and Government from all fifteen (15) countries in the ECOWAS adopted the Protocol creating the organization. The Protocol, which was subsequently ratified by each government in the sub-region, grants WAHO status as a Specialized Agency of ECOWAS and describes the organization's mission as follows: «The objective of the West African Health Organization shall be the attainment of the highest possible standard and protection of health of the peoples in the region through the harmonisation of the policies of the Member States, pooling of resources, and cooperation with one another and with others for a collective and strategic combat against the health problems of the sub-region.»

The WAHO has taken actions under its current medicines and vaccines programme to facilitate access to essential and quality medicines, vaccines and essential health products and reduce the use of illicit drugs and counterfeiting in the region.

In 2010, WAHO developed the Common Technical Documents on Medicines Registration Harmonization for the Economic Community of West African States (ECOWAS)<sup>2</sup> for the purpose of harmonizing medicine registration and regulation within the region. At the same time, the West African Economic and Monetary Union (known as UEMOA: Union Économique et Monétaire Ouest-Africaine) developed Annexes to regulation N°06/2010/CM/UEMOA describing the Approval Procedures for Pharmaceuticals for Human Use in the UEMOA Member States.

The UEMOA is an organization of eight West African states established, in 1994, to promote economic integration among countries that share the CFA franc as a common currency. In July 2005, the UEMOA Council of Ministers adopted a regulation aimed at establishing a harmonized regulatory framework for pharmaceuticals.

The project to harmonize the ECOWAS and the UEMOA documents was initiated in 2015 and supported by the Bill and Malinda Gates Foundation and facilitated by the Regulatory Systems Strengthening Group at the World Health Organization. In December 2016 a draft registration guideline in the Common Technical Document (CTD) format was created by merging the ECOWAS and the UEMOA documents. The draft was reviewed at a validation workshop held in Abidjan, Cote d'Ivoire on April 18-19, 2016. This second draft for the Registration of Generic Pharmaceuticals for Human Use in the CTD format for the Economic Community of West African States reflects the decision to narrow the scope of the document to Multisource (generic) pharmaceutical products. This draft also reflects the comments received during the Abidjan workshop.

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<sup>2</sup> Common Technical Documents on Medicines Registration Harmonization for The Economic Community Of West African States (ECOWAS), September 2010.

## ACKNOWLEDGEMENTS

This document was produced by the West African Health Organization (WAHO)'s Essential Medicines and Vaccines Programme in the Public Health and Research (DPHR) Department under the frameworks of the Sahel Women's Empowerment and Demographic Dividends (SWEDD) and West African Medicines Regulatory Harmonization (WA-MRH) Projects, linked to the African Medicines Regulatory Harmonization and Global Medicines Regulatory Harmonization Initiatives, hugely supported by technical and financial partners, notably among which are the World Health Organization (WHO), African Union Development Agency (AUDA-NEPAD), World Bank, Bill and Melinda Gates Foundation (BMGF), Swissmedic, and USAID.

This document has been developed on the basis of valuable inputs made during the consultation, and developmental phases as well as regional stakeholders' validation meetings.

We would like to express our gratitude to all institutions, partners and persons who have in numerous ways supported WAHO to strengthen and improve the accessibility of quality, safe, efficacious and affordable essential medicines in the ECOWAS region. A special thanks goes to the Union Economique et Monétaire Ouest Africaine (UEMOA) that supported WAHO by agreeing in 2014, on a single integrated roadmap for better regional coordination of medicines regulatory harmonization in West Africa.

Special appreciation goes particularly to the partners who provided their expertise and supported WAHO to develop the ECOWAS harmonized Common Technical Document (CTD), the WHO Team: Samvel Azatyan, Gabriela Zenhausern and Consultant Brigitte Zirger, UEMOA Team: Mahamane Hamidine and Carmelle Hounnou; NEPAD Team: Aggrey Ambali, Margareth Ndomondo-Sigonda, Hudu Mogtari; World Bank Team: Andreas Seiter, Aissatou Diack, Christophe Lemiere, Benjamin Botwe and Cassandra De Souza; and David Mukanga of BMGF

Sincere gratitude also goes to the WAHO Team for their relentless effort to ensure that the harmonized CTD gets developed, validated and adopted by the Assembly of Health Ministers: Carlos Brito, the Director of the Department of Public Health and Research, Sybil Nana Ama Ossei- Agyeman-Yeboah, the Programme Officer responsible for Essential Medicines and Vaccines in WAHO, and the WA-MRH Team: Assi Bernard Assi, Oluwafunmike Sopein-Mann and Pierre Kpatcha Tchamdja.

We wish to appreciate and to thank also the Heads of the National Medicines Regulatory Authorities (NMRAs) and WA-MRH Focal Persons in the fifteen (15) ECOWAS Member States.

We also thank the national, regional, continental and global Pharmaceutical Industrial Associations: Pharmaceutical Manufacturers Group of Manufacturing Association of Nigeria (PMG-MAN), Pharmaceutical Manufacturers Association of Ghana (PMAG), West African Pharmaceutical Manufacturers Association (WAPMA), African Pharmaceutical Manufacturers Association (FAPMA), and International Federation Pharmaceutical Manufacturers Association (IFPMA) and all contributors from ECOWAS Member States, numerous other Partners and the Civil Society who diligently reviewed and validated the harmonized CTD and gave valuable suggestions.

It is our expectation that the population of the ECOWAS region and the Pharmaceutical sector will benefit greatly from this ECOWAS harmonized Common Technical Document for registration of pharmaceutical for human use.

Prof. Stanley OKOLO

Director -General

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## LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
ATC	Anatomical, Therapeutical and Chemical Classification
CEP	Certificate of Suitability issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM)
CPP	Certificate of Pharmaceutical Product
CTD	Common Technical Document
DMF	Drug Master File
ECOWAS	Economic Community for West African States
FPP	Finished Pharmaceutical Products
GMP	Good Manufacturing Practices
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation of Technical Requirements for the Registration of Medicines for human use
INN	International Non-Proprietary Name
MA	Market Authorization
NCE	New Chemical Entities
NMRA	National Medicines Regulatory Authority
OTC	Over the Counter Medicines
PIL	Patient Information Leaflet
POM	Prescription-only Medicines
SmPC	Summary of Product Characteristics
WAHO	West African Health Organization
WHO	World Health Organization



## GLOSSARY / DEFINITIONS

### ***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.

### ***Authorized person***

The person recognized by the National Regulatory Authority as having the responsibility for ensuring that each batch of finished product has been manufactured, tested and approved for release in compliance with the laws and regulations in force in that country.

### ***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.

### ***Bio-equivalence:***

Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or pharmaceutical alternatives, and their bio-availabilities, in terms of peak (C<sub>max</sub> and T<sub>max</sub>) 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<sup>3</sup>.

### ***Bulk Product:***

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

### ***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

### ***Finished product***

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.

### ***Manufacture***

All operations of purchase of materials and products, production, quality control, release, storage and distribution of pharmaceutical products, and the related controls.

<sup>3</sup> WHO, THE BLUE BOOK, Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products, A manual for National Medicines Regulatory Authorities (NMRAs). 2nd EDITION

**Marketing authorization (product license, registration certificate)**

An official document issued by a competent medicines regulatory authority for the purpose of marketing or free distribution of the product after evaluations for safety, efficacy and quality.

**Master formula**

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

**Master record**

A document or set of documents that serve as a basis for the batch documentation.

**Multisource (Generic) Product**

Multisource pharmaceutical products are pharmaceutically equivalent products that may or may not be therapeutically equivalent. Only multisource pharmaceutical products that are therapeutically equivalent are interchangeable.

**Pharmaceutical product**

Any material or product intended for human use presented in its finished dosage form or as a starting material for use in such a dosage form that is subject to control by pharmaceutical legislation.

**Production**

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

**Specification**

List of detailed requirements with which the products or materials used or obtained during manufacture have to conform. It serves as a basis for quality evaluation.

**Standard Operating Procedure (SOP)**

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material (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.

## INTRODUCTION

This document provides guidance for the preparation of a product dossier (PD)/application in the Common Technical Document (CTD) format for the Registration of Medicines for Human Use in the Economic Community of West African States (ECOWAS).

The document describes how to organize and format the product dossier; it does not describe what information, studies or data are required. Therefore, when preparing a regulatory dossier, it is necessary to consult relevant guidance documents on technical (data) requirements.

The use of the CTD allows applicants to prepare dossiers for the NMRAs of ECOWAS without unnecessarily reformatting information that may already have been submitted to other international regulatory authorities. It will reduce the cost of both submission and assessment, support collaboration and information exchange between regulators, and increase the access to critical and essential medicines in the ECOWAS region.

The document is based on the International Council for Harmonization guidelines for Technical Requirements for Registration of Pharmaceuticals for Human Use, namely ICH M4, ICH M4Q, ICH M4S, and ICH M4E. This guideline should be read in conjunction with other applicable WHO and ICH reference documents that provide further guidance and recommendations on the topic-specific content requirements in Modules 2 to 5. References to these will be provided throughout this document.

## GENERAL PRINCIPLES OF PRESENTATION

This section provide an overview of the physical presentation of the regulatory dossier in CTD format. Table 1 outlines the modular structure and main headings that should be used.

Some headings and/or subheadings may not be applicable to certain dossiers, such as those for multisource (generic) drugs or variations. When no information is required in a specific section or subsection, that heading or subheading should be omitted. The numbering of an omitted section should not be reused for another section.

Insert the corresponding sentence of the document in French

### LANGUAGE

There are three official languages in the ECOWAS region. These are English, French and Portuguese. Applications for products seeking a region-wide market authorization shall be submitted in English. However, the summary product characteristics, labelling and packaging information shall be submitted in all the three official languages of the region (English, French and Portuguese).

Where applicants wish to register the product in a specific country, the official language of that country SHALL be used for the application, the technical package and supporting documents.

In cases where there is the need to translate a document from its original language into the other languages used in the region, the accuracy of the translations is the responsibility of the applicant.

### DATA PRESENTATION

Dossiers should be submitted in separately bound volumes for the different parts but shall be numbered serially (e.g. Vol.1 of 2) for ease of reference.

Text and tables should be prepared using margins that allow the document to be printed on A4 and 80g/m<sup>2</sup> paper. The left-hand margin should be sufficiently large that information is not obscured by the method of binding. Font sizes for text, tables, flow diagrams and floor maps should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font is recommended for narrative text.

All pages shall be numbered appropriately with the format 'page x of y' to facilitate easy reference by evaluators. Each section of the dossier must have a table of content and must be accurately referenced. Acronyms and abbreviation should be defined the first time they are used in each part.

### REFERENCES AND TEXTS

International standards for citing references in any parts of the dossier must be followed. The latest edition of any reference source, specifying the year of publication must be used.

Literature references should be cited in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journals Editors (ICMJE). Acronyms and abbreviations should be defined the first time they are used in each module.

Where necessary, especially for analytical methods, specifications and procedures, copies of the relevant portions of the reference source(s) must be included.

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

## STRUCTURE OF THE CTD FORMAT

Information within the CTD is organized into a series of structured documents which are in turn organized into modules.

**Table 1 : Main Section Headings in the Common Technical Document (CTD) Format**

Number	Title and Main Section Headings
	<b>Module 1: Administrative and Product Information</b>
1.0	Table of Contents (Modules 1 to 5)
1.1	Correspondence
1.2	Administrative Information
1.3	Product Information
1.4	Regional Requirements
1.5	Clinical Trial Information
1.A	Appendix
	<b>Module 2: Common Technical Document (CTD) Summaries</b>
2.1	CTD Table of Contents (Modules 2 to 5)
2.2	CTD Introduction
2.3	Quality Overall Summary
2.4	Nonclinical Overview
2.5	Clinical Overview
2.6	Nonclinical Written and Tabulated Summaries
2.7	Clinical Summary
	<b>Module 3: Quality</b>
3.1	Table of Contents of Module 3
3.2	Body of Data
3.3	Literature References
	<b>Module 4: Nonclinical Study Reports</b>
4.1	Table of Contents of Module 4
4.2	Study Reports
4.3	Literature References
	<b>Module 5: Clinical Study Reports</b>
5.1	Table of Contents of Module 5
5.2	Tabular Listing of All Clinical Studies
5.3	Clinical Study Reports
5.4	Literature References
Red text indicates sections that are not normally needed for a generic drug	

## MODULE 1: ADMINISTRATIVE AND PRODUCT INFORMATION

Module 1 should contain all administrative documents (for example, application forms, certifications, labeling and general correspondence, etc. The documents should be organized in the order below.

### 1.0 TABLE OF CONTENTS (ToC)

The Table of Contents (ToC) for the entire regulatory dossier should be placed in this section. It should list all documents included in Modules 1-5. A module-specific ToC is included with each Module.

### 1.1 CORRESPONDENCE

All correspondence-related documents submitted to the regulatory authority are to be placed in Module 1.1 unless otherwise indicated. Scientific information is not to be included in this Module.

#### 1.1.1 Cover Letter

A cover letter should accompany any data being submitted to the regulatory authority. The cover letter should clearly state what is being submitted, including reference to the request letter (if applicable) and a brief description of the package.

The cover letter should not contain any scientific information.

Note that the Question and Answer (Q and A) responses related to correspondence issued by the regulatory authority and the Note to Reviewer are assigned a specific location (1.1.3 and 1.1.6) and should not be included in the cover letter.

Any cross-referenced regulatory document should be clearly stated in the cover letter, and the following information should be included:

- application type, specify whether new, renewal or variation
- NMRA application number (issued by the NMRA)
- date of regulatory authorization if applicable
- brand name, DCI, dosage, presentation, dosage form
- manufacturer's name
- Applicant's name
- Number of samples submitted

A sample cover letter is provided in Annex B: FORMS

#### 1.1.2 Copy of Correspondence Issued by the Regulatory Authority

A copy of the correspondence issued by the regulatory authority, being responded to should be placed in this section. This includes (but is not limited to) the following:

- A request for additional information (during screening or evaluation);
- A negative decision (e.g., deferrals or rejections).

#### 1.1.3 Information Solicited by the Regulatory Authority

Solicited information is defined as information requested by the regulatory authority (copy of the regulator's correspondence is placed in section 1.1.2). Responses to these requests are to be provided in Question and Answer format, and placed in this section. The answers should summarize the response and cross-reference the supporting data that is to be placed in the appropriate Module of the regulatory document. No supporting data in connection with the answers is to be provided in this section.

#### **1.1.4 Meeting Information**

Any meeting related information and documentation, with the exception of an Appeal meeting, are to be placed in this section. This includes (but is not limited to) the following:

- meeting information package;
- proposed meeting agenda;
- Presentation slides;
- Meeting minutes.

#### **1.1.5 Request for Appeal Documentation**

Any person aggrieved by a decision in relation to any application for marketing authorization of a pharmaceutical product may within two (2) months from the date of notice of the decision, make representations in writing to WAHO or the appropriate NMRA and submit additional data to support the appeal.

Any documentation required as part of a manufacturer's Request to Appeal a regulatory decision is to be placed in this section.

#### **1.1.6 General Note to Reviewer**

The Note to Reviewer should be used to facilitate the review. These comments are NOT to be included in the cover letter.

Notes relating to the entire regulatory dossier (e.g., advising that the product is referred to by a foreign trade name throughout the regulatory document) should be placed in this section.

Notes relating to a specific section of the regulatory document should be placed at the beginning of each pertinent section. For example, this note can be used to identify changes in a section and/or document.

## **1.2 ADMINISTRATIVE INFORMATION**

### **1.2.1 Application Forms**

Completed and signed application forms should be placed in this section.

(See Model Application Form in Annex B)

### **1.2.2 Fee Forms**

Application fees shall be paid for each application submitted. This shall be in the form prescribed by the applicable NMRA or WAHO.

Completed fee forms (proof/evidence of payment) should be placed in this section.

(See Model Fee Form in Annex B)

### **1.2.3 Certification and Attestation Forms**

Completed and signed forms are to be placed in this section. These include, but are not limited to, the following:

- Certification of Suitability to the Monographs of the European Pharmacopoeia (CEP) issued by the European Directorate for the Quality of Medicines and Healthcare (EDQM),
- World Health Organization Confirmation of Prequalification (WHO-CPQ) – where applicable.
- The export authorization if the product is not registered in the country of manufacture OR a Certificate of Pharmaceutical Product issued by the competent authority in the country of manufacture
- The Product Certificate issued by the NMRA;
- Any and all Certificates of analysis as required in the quality guidance. (In reference to the module 3)

#### **1.2.4 Compliance and Site Information**

Submit any that apply.

##### 1.2.4.1 Good Manufacturing Practices

Good Manufacturing Practices (GMP) compliance information should be placed in this section. Regulatory GMP compliance status issued by other jurisdictions, including Date of last GMP and/or pre-approval inspection, and any observation-related information should also be placed in this section.

##### 1.2.4.2 Other Compliance and Site Information Documents

Any other regulatory compliance and site-related information which is not currently mentioned should be placed in this section.

#### **1.2.5 Authorization for Sharing Information**

Letters authorizing the regulatory authority to access Drug Master Files (DMFs)/ active pharmaceutical ingredient master files or Site Reference files (SRF) should be included here. See model letter of access in ANNEX B.

#### **1.2.6 Regional and International Regulatory Status**

Provide evidence on registration status of the proposed product(s) and, approved indications in the country of origin, other parts of the ECOWAS region and in other countries/regions.

Provide evidence if the API or Finished Pharmaceutical Product is prequalified by the WHO.

Depending upon the status of the product this may include, but not be limited to, the following:

- International / regional registration, review and/or marketing status, including date of filing, approval of product or supplemental changes in other jurisdictions, information regarding the withdrawal, stop of sale and/or market recall;
- Foreign refusals;
- Foreign clinical trial status;
- Date of the first registration of the product for all approved indications;
- Confirmation of filing or the date(s) of approval or withdrawal.
- Certification issued by the competent authority for the country of product origin that the product is marketed in the country of origin
- Certification issued by the applicable competent authority for the wholesale price excluding tax in the country where the product is marketed.

#### **1.2.7 Trademark & Intellectual Property Information**

Application for the registration of medicines at the WAHO or country level may be made by the manufacturer of the product, or the license/ patent holder. In situations where applications are submitted by other entities, a duly authenticated power of attorney from the manufacturer or license holder shall be submitted.

#### **1.2.8 Post-Authorization Information**

Periodic Safety Update Reports (PSURs) are to be filed in this section as applicable.

#### **1.2.9 Other Administrative Information**

This section is for any administrative information that does not have a designated location in the CTD format. This section should NOT contain any scientific information.

Requests for bio-waivers are submitted in this section. Justification for the request for bio-waivers shall be submitted as per Guidance on Bio-waivers.



## 1.3 PRODUCT INFORMATION

The content of the Summary of Product Characteristics (SmPC), the Patient Information Leaflet and all labels in any of the 3 official languages should be the same.

See Model Product Information Templates provided in ANNEX A

### 1.3.1 Summary of Product Characteristics (Prescribing Information)

A copy of the Summary of Product Characteristics (SmPC) is to be placed in this section. This includes all alternate language SmPCs.

When revisions are requested during the course of an evaluation, an annotated version of the revised SmPC is required. The annotations should identify all changes made, either in relation to the last approved SmPC or in response to a request made by the regulatory authority.

### 1.3.2 Patient Information Leaflet

A copy of the Patient Information Leaflet (PIL) is to be placed in this section.

### 1.3.3 Container Labels

All container labels, including the inner and outer labels, should be provided in this section.

This should include the labels for all strengths, dosage forms and reconstitution diluents.

When additional revisions are requested during the course of the review, an annotated version of the revised label may be requested, and should be placed in this section.

### 1.3.4 Foreign Labelling

If the drug product has been marketed outside the region, the applicant shall supply the SmPC approved for WHO prequalified products and those marketed elsewhere in the ECOWAS or other African regions, must clearly translate the labelling into the three official languages of ECOWAS

### 1.3.5 Reference Product Labelling

For multisource (generic) products, the SmPC for the Reference Product(s) is to be placed in this section.

## 1.4 REGIONAL SUMMARIES

### 1.4.1 Bioequivalence Trial Information

The completed Bioequivalence Trial Information Form (BTIF) for all pivotal comparative bioavailability (bioequivalence) studies should be placed in this section.

See BTIF Template provided in ANNEX C

## 1.A APPENDIX

### MODULE 1.A.1 ELECTRONIC DOCUMENTS

Electronic versions of applications are encouraged either in searchable Portable Document Format (PDF) or Word. This electronic document should be saved to a CD-ROM or other acceptable storage medium.

All electronic media submitted to support the drug regulatory document should be placed in this section.

## MODULE 2: COMMON TECHNICAL DOCUMENT (CTD) SUMMARIES

Module 2 includes the following 7 sections. For multisource (generic) pharmaceutical products, Modules 2.4-2.7 are not usually needed.

- 2.1 CTD Table of Contents (Modules 2-5)
- 2.2 CTD Introduction
- 2.3 Quality Overall Summary
- 2.4 Nonclinical Overview
- 2.5 Clinical Overview

### 2.1 CTD TABLE OF CONTENTS (MODULE 2-5)

The table of contents for Module 2 to 5 should be provided.

### 2.2 CTD INTRODUCTION

The introduction should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It should briefly describe the contents of the Modules 2 to 5 with appropriate cross-references to them.

### 2.3 QUALITY OVERALL SUMMARY

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.

Complete the QOS-PD Template in Annex C following the guidance in this section.

Refer to ICH M4Q (R1)

#### 2.3.S DRUG SUBSTANCE

For a drug product containing more than one drug substance, the information in module 2.3.S.1 to 2.3.S.7 should be submitted for each drug substance, clearly identifying the substance name and manufacturer in the title of each module.

##### **2.3.S.1 General Information (name, manufacturer)**

Include information from Module 3.2.S.1

##### **2.3.S.2 Manufacture (name, physical address, i.e., site)**

Include information from Module 3.2.S.2

Information on the manufacturer,

- Provide the name, address and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing.
- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality; this could be presented as a flow diagram.
- A flow diagram, as provided in 3.2.S.2.2;
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the API, as described in 3.2.S.2.3;
- Highlight critical process intermediates, as described in 3.2.S.2.4;
- A description of process validation and/or evaluation, as described in 3.2.S.2.5.

##### **2.3.S.3 Characterisation (name, manufacturer)**

A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1, should be included.

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

#### **2.3.S.4 Control of Drug Substance (name, manufacturer)**

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

Specification from 3.2.S.4.1 should be provided.

A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate, should be provided.

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

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

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

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

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

This section should include a summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions, retest date or shelf-life, where relevant, as described in 3.2.S.7.1.

The post-approval stability protocol, as described in 3.2.S.7.2, should be included.

A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

### **2.3.P FINISHED PHARMACEUTICAL PRODUCT**

#### **2.3.P.1 Description and Composition of the Drug Product (name, dosage form)**

Information from 3.2.P.1 should be provided.

Composition from 3.2.P.1 should be provided.

#### **2.3.P.2 Pharmaceutical Development (name, dosage form)**

A discussion of the information and data from 3.2.P.2 should be presented.

A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

#### **2.3.P.3 Manufacture (name, dosage form)**

Information from 3.2.P.3 should include:

- Information on the manufacturer.
- A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality.
- A flow diagram, as provided under 3.2.P.3.3.
- A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5.

#### **2.3.P.4 Control of Excipients (name, dosage form)**

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

#### **2.3.P.5 Control of Drug Product (name, dosage form)**

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided.

Specification(s) from 3.2.P.5.1 should be provided.

A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate should be included.

### **2.3.P.6 Reference Standards or Materials (name, dosage form)**

Information from 3.2.P.6 (tabulated presentation, where appropriate) should be included.

### **2.3.P.7 Container Closure System (name, dosage form)**

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

### **2.3.P.8 Stability (name, dosage form)**

A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data should be included. Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.

A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate, should be included.

The post-approval stability protocol, as described in 3.2.P.8.2, should be provided.

## **2.3.A Appendices**

## **2.3.R Regional Information**

## **2.4 NON-CLINICAL OVERVIEW**

The Nonclinical Overview should provide an integrated overall analysis of the information in the Module 4. In general, the Nonclinical Overview should not exceed 30 pages.

The Nonclinical Overview should be presented in the following sequence:

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

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

ICH M4S (R2) Module 2.4 provides guidance for the contents of the Non-clinical Overview. The non-clinical information in Module 2.4 and Module 4 is not normally required for multisource (generic) drug products. However in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

## **2.5 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 (e.g., pertinent animal data or product quality issues that may have clinical implications).

The clinical overview should be presented in the following order:

- Table of Contents
- 2.5.1 Product Development Rationale
- 2.5.2 Overview of Biopharmaceutics
- 2.5.3 Overview of Clinical Pharmacology
- 2.5.4 Overview of Efficacy
- 2.5.5 Overview of Safety
- 2.5.6 Benefits and Risks Conclusions
- 2.5.7 Literature References

ICH M4E (R1) Module 2.5 provides guidance for the contents of the Clinical Overview.

## 2.6. NONCLINICAL WRITTEN AND TABULATED SUMMARIES

### Nonclinical Written Summaries

#### Introduction

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

The sequence and content of the Nonclinical Written Summary sections are described below. It should be emphasised that no guideline can cover all eventualities, and common sense and 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 devaluation 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.

### General Presentation Issues

#### Order of Presentation of Information within Sections

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

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

Species should be ordered as follows:

- Mouse
- Rat
- Hamster
- Other rodent
- Rabbit
- Dog
- Non-human primate
- Other non-rodent mammal
- Non-mammals

Routes of administration should be ordered as follows :

- The intended route for human use
- Oral
- Intravenous
- Intramuscular

- Intraperitoneal
- Subcutaneous
- Inhalation
- Topical
- Other

### **Use of Tables and Figures**

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

To allow authors flexibility in defining the optimal structure for the Written Summaries, tables and figures should preferably be included within the text. Alternatively, they could be grouped together at the end of each of the Nonclinical Written Summaries. Throughout the text, reference citations to the Tabulated Summaries should be included, in the following format: (Table X.X, Study/Report Number).

### **Length of Nonclinical Written Summaries**

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

### **Sequence of Written Summaries and Tabulated Summaries**

The following order is recommended:

- Introduction
- Written Summary of Pharmacology
- Tabulated Summary of Pharmacology
- Written Summary of Pharmacokinetics
- Tabulated Summary of Pharmacokinetics
- Written Summary of Toxicology
- Tabulated Summary of Toxicology

Refer ICH M4S\_R2 for detailed discussion of content of the non-clinical written and tabulated summaries.

## **2.7. CLINICAL SUMMARY**

### **Preamble**

The Clinical Summary is intended to provide a detailed, factual summarisation of all of the clinical information in the Common Technical Document. This includes information provided in ICH E3 clinical study reports; information obtained from any meta-analyses or other cross-study analyses for which full reports have been included in Module 5; and post-marketing data for products that have been marketed in other regions.

The comparisons and analyses of results across studies provided in this document should focus on factual observations. In contrast, the CTD Clinical Overview document should provide critical analysis of the clinical study program and its results, including discussion and interpretation of the clinical findings and discussion of the place of the test drug in the armamentarium.

The length of the Clinical Summary will vary substantially according to the information to be conveyed, but it is anticipated that (excluding attached tables) the Clinical Summary will usually be in the range of 50 to 400 pages.

## **Table of Contents**

### **2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods**

- 2.7.1.1 Background and Overview
- 2.7.1.2 Summary of Results of Individual Studies
- 2.7.1.3 Comparison and Analyses of Results Across Studies
- 2.7.1.4 Appendix

### **2.7.2 Summary of Clinical Pharmacology Studies**

- 2.7.2.1 Background and Overview
- 2.7.2.2 Summary of Results of Individual Studies
- 2.7.2.3 Comparison and Analyses of Results Across Studies
- 2.7.2.4 Special Studies
- 2.7.2.5 Appendix

### **2.7.3 Summary of Clinical Efficacy**

- 2.7.3.1 Background and Overview of Clinical Efficacy
- 2.7.3.2 Summary of Results of Individual Studies
- 2.7.3.3 Comparison and Analyses of Results Across Studies
- 2.7.3.4 Analysis of Clinical Information Relevant to Dosing Recommendations
- 2.7.3.5 Persistence of Efficacy and/or Tolerance Effects
- 2.7.3.6 Appendix

### **2.7.4 Summary of Clinical Safety**

- 2.7.4.1 Exposure to the Drug
- 2.7.4.2 Adverse Events
- 2.7.4.3 Clinical Laboratory Evaluations
- 2.7.4.4 Vital Signs, Physical Findings, and Other Observations Related to Safety
- 2.7.4.5 Safety in Special Groups and Situations
- 2.7.4.6 Post-marketing Data
- 2.7.4.7 Appendix
- 2.7.5 Literature References
- 2.7.6 Synopses of Individual Studies

Refer ICH M4E\_R1 for detailed discussion of content of the clinical summary.

## MODULE 3: QUALITY

The Quality module follows the structure and illustrative explanations that are outlined in ICH M4Q (R1).

### 3.1 TABLE OF CONTENTS (MODULE 3)

The table of contents should give the location of each study report in Module 3

### 3.2. S BODY OF DATA - DRUG SUBSTANCE

The following information may be submitted as information for the API as applicable:

- Option 1 - Full details in the product dossier
- Option 2 – Confirmation that Drug Substance (API) is pre-qualified by the WHO
- Option 3 - A Certificate of Suitability of European Pharmacopeia (CEP).

For a drug product containing more than one drug substance, the information should be submitted for each drug substance.

Where reference is made to a CEP, the applicant must provide a letter of access from the CEP holder. The letter of access should be provided in Module 1.2.5. Evidence of WHO Pre-qualification should be provided in Module 1.2.6.

Refer to WHO Technical Report Series, No. 970 Annex 4

Option 1	Option 2 API-PQP by WHO	Option 3 CEP
3.2.S.1.3 General properties	Yes	Yes
3.2.S.1 Manufacture		
3.2.S.2.1 Manufacturer	Yes if sterility of FPP depends on sterile API	
3.2.S.2.2 Description of manufacturing process and process controls		
3.2.S.2.3 Control of materials		
3.2.S.2.4 Controls of critical steps and intermediates		
3.2.S.2.5 Process validation and/or Evaluation		
3.2.S.2.6 Manufacturing Process development		
3.2.S.3.1 Elucidation of structure and other	Yes	Yes
3.2.S.4 Control of Drug Substance		
3.2.S.4.1 Specification	Yes	Yes
3.2.S.4.2 Analytical procedures and validation	Yes	Yes
3.2.S.4.3 Validation of Analytical Procedures	Yes	Yes
3.2.S.4.4 Batch analysis	Yes	Yes
3.2.S.5 Reference standards or materials	Yes	Yes
3.2.S.6 Container-closure system		Yes
3.2.S.7 Stability		
3.2.S.7.1 Stability Summary and Conclusion	Yes If longer retest period or higher storage temper- atures than the prequalified API	Yes If longer retest period or higher storage temperatures than the prequalified API
3.2.S.7.2 Post-approval stability Protocol and stability commitment		
3.2.S.7.3 Stability Data		



### **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 approved non-proprietary name(s);
- Chemical Abstracts Service (CAS) registry number.

#### **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.

#### **3.2.S.1.3 General Properties (name, manufacturer)**

The structure, molecular formula, molecular weight and structural formula are specified. The chiral centres if any are identified.

Refer to ICH Guidelines: Q6A and Q6B

### **3.2.S.2 Manufacturer (name, manufacturer)**

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

State the name and street address of each facility where manufacture (synthesis, production) of API occurs, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided. Provide phone number(s) and E-mail addresses. Include any alternative manufacturers. Provide a valid manufacturing Authorization for the production of APIs. If available, attach a certificate of GMP compliance. (Submitted in Module 1.2.4)

#### **3.2.S.2.2 Description of Manufacturing Process and Process Controls (name, manufacturer)**

Description of the manufacturing process and the summary diagram of the active substance.

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

Reprocessing steps should be identified and justified and any data to support this justification should be either referenced.

Refer to ICH Guidelines: Q5A, Q5B, and Q6B

#### **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.

Refer ICH Guidelines: Q6A and Q6B

#### **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.

Refer to ICH Guidelines: Q6A and Q6B

#### 3.2.S.2.5 Process Validation and/or Evaluation (name, manufacturer)

Description of the validation process and evaluation of the manufacturing method.

#### 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 drug substance used in producing non-clinical, stability, scale-up, pilot, and , if available, production scale batches.

Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Refer to ICH Guideline: Q3A

### **3.2.S.3 Characterisation (name, manufacturer)**

Describe the method of Characterization

#### 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 be included.

Refer to ICH Guideline: Q6A

#### 3.2.S.3.2 Impurities (name, manufacturer)

Information on impurities should be provided.

Refer to ICH Guidelines: Q3A, Q3C, Q5C, Q6A, and Q6B

### **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.

Refer to ICH Guidelines Q2 (R1) and Q6B, and WHO Technical Report Series, No. 970-Annex 4

#### 3.2.S.4.2 Analytical Procedures (name, manufacturer)

The analytical procedures used for testing the drug substance should be provided.

Refer to ICH Guidelines: Q2 (R1)

#### 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 drug substance should be provided.

Refer to ICH Guidelines: Q2 (R1) and Q6B

#### 3.2.S.4.4 Batch Analyses (name, manufacturer)

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

Refer to ICH Guidelines: Q3A, Q3C, Q6A, and Q6B

#### 3.2.S.4.5 Justification of Specification (name, manufacturer)

Justification for the drug substance specification should be provided.

Refer to ICH Guidelines: Q3A, Q3C, Q6A and Q6B

### **3.2.S.5 Reference Standards or Materials (name, manufacturer)**

Information on the reference standards or reference materials used for testing of the drug substance should be provided.

Refer to ICH Guidelines: Q6A and Q6B

### **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-compendia 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 drug substance, including sorption to container and leaching, and/or safety of materials of construction.

Provide a certificate of analysis for the container closure materials in module 1.2.3

Refer to WHO Technical Report Series, No. 902 Annex 9

### **3.2.S.7 Stability (name, manufacturer)**

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

The types of studies conducted, protocols used, and the results of the studies should be summarized. The summary should include results, for example, from forced degradation studies and stress conditions, as well as conclusions with respect to storage conditions and retest date or shelf-life, as appropriate.

Refer to ICH Guidelines: Q1A, Q1B, and Q5C, and WHO Technical Report Series, No. 953 Annex 9

#### **3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment (name, manufacturer)**

The post-approval stability protocol and stability commitment should be provided.

Refer to documents: ICH Q1A (20), Q1B (22), Q1D (24), Q1E (23),

WHO Technical Report Series, No. 953, Annex 2

#### **3.2.S.7.3 Stability Data (name, manufacturer)**

Results of the stability studies (e.g. forced degradation studies and stress conditions) should be presented in an appropriate format such as tabular, graphical narrative. Information on the analytical procedures used to generate the data and validation of the procedures should be included.

Refer to ICH Q1A, Q1B, Q1D, Q1E, Q2 (R1), and

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products, WHO Technical Report Series, No. 953, Annex 2, 2009

### **3.2.P Body of Data – Finished Drug Product (name, dosage form)**

#### **3.2.P.1 Description and Composition of the Drug Product (name, dosage form)**

A description of the FPP or drug product and its composition should be provided.

The information provided should include, for example:

- A description of the dosage form;
- Composition i.e., list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. Compendia monographs or manufacturers specifications)
- Description of accompanying reconstitution diluent(s); and
- Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

Note: For a drug product supplied with reconstitution diluents(s) the information on the diluent(s) should be provided in a separate part "P" as appropriate.

Refer to ICH Guidelines: Q6A and Q6B

### ***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.

Refer to ICH Guidelines: Q6A and Q6B, and WHO Technical Report Series, No. 970, Annex 4

#### ***3.2.P.2.1 Components of the Drug Product (name, dosage form)***

##### ***3.2.P.2.1.1 Drug Substance (name, dosage form)***

The compatibility of the drug substance with excipients listed in 3.2.P.1 should be discussed. Additionally, key physicochemical characteristic (e.g. water content, solubility, and particle size distribution, polymorphic or solid state form) of the drug substance that can influence the performance of the drug product should be discussed.

For fixed dose combination products, the compatibility of drug substances with each other should be discussed.

##### ***3.2.P.2.1.2 Excipients (name, dosage form)***

The choice of excipients, their concentration and their characteristics that can influence the drug product performance should be discussed relative to their respective functions.

#### ***3.2.P.2.2 Drug Product (name, dosage form)***

##### ***3.2.P.2.2.1 Formulation Development (name, dosage form)***

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) described 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.

##### ***3.2.P.2.2.2 Overages (name, dosage form)***

Any overages in the formulations(s) should be justified

##### ***3.2.P.2.2.3 Physicochemical and Biological Properties (name, dosage form)***

##### ***3.2.P.2.2.3 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. Differences between the manufacturing processes used to produce pivotal clinical batches and the process described that can influence the performance of product should be discussed.

##### ***3.2.P.2.2.4 Container Closure System (name, dosage form)***

The suitability of the container closure system used for the storage, transportation (shipping) and use of the drug product should be discussed. This discussion should consider, e.g. choice of material, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption of 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 drug product).

#### 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.

#### 3.2.P.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, sorption on injection vessels) stability should be addressed to provide appropriate and supportive information for the labelling.

### **3.2.P.3 Manufacture (name, dosage form)**

#### 3.2.P.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. Include, for example, production, sterilization, packaging and quality control.

For each site where the major production step(s) is/are carried out, attach (in module 1.2.6) a valid manufacturing authorization for pharmaceutical production. Attach an original WHO-type certificate of GMP issued by the competent authority.

#### 3.2.P.3.2 Master Formula (name, dosage form)

A recent master formula should be provided that includes a list of components of the dosage form to be used in the manufacturing process, their amounts per batch basis including overages, and a reference to their quality standards.

#### 3.2.P.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 blend, 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 case, environmental conditions (e.g. experimentally documented temperature and relative humidity for hygroscopic FPPs) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section (3.2.P.3.3).

Refer to ICH Guideline: Q6B

#### 3.2.P.3.4 Controls of Critical Steps and Intermediates (name, dosage form)

Critical steps: Test and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps 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.

Refer to ICH Guidelines: Q2 (R1), Q6A, and Q6B

#### 3.2.P.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).

Refer to ICH Guideline: Q6B

#### **3.2.P.4 Control of Excipients (name, dosage form)**

##### 3.2.P.4.1 Specifications (name, dosage form)

The specifications for excipients should be provided.

Refer to ICH Guideline: Q6A and Q6B

##### 3.2.P.4.2 Analytical Procedures (name, dosage form)

The certificate of analysis must be provided.

The analytical procedures used for testing the excipients should be provided where appropriate.

Refer to ICH Guidelines: ICH Q2 (R1)

##### 3.2.P.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.

Refer to ICH Guidelines: ICH Q6B and ICH Q2 (R1)

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

Justification for the proposed excipient specifications should be provided, where appropriate.

Refer to ICH Guidelines: Q3C and Q6B

##### 3.2.P.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. (Details in 3.2.A.2).

Refer to ICH Guidelines: Q5A, Q5D, and Q6B

##### 3.2.P.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 (non-clinical and/or clinical) should be provided according to the API and/or FPP format. (Details in 3.2.A.3).

#### **3.2.P.5 Control of Drug Product (name, dosage form)**

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

The specification(s) for the drug product should be provided.

Refer to ICH Guidelines: Q3B, Q6A and Q6B

A list of general characteristics, specific standards, tests and limits for results for the FPP must be provided. Two separate sets of specifications may be set out; at manufacture (at release) and at the end of shelf life. Justification for the proposed specification should be provided.

##### 3.2.P.5.2 Analytical Procedures (name, dosage form)

The analytical procedures used for testing the FPP should be provided.

Reference ICH Q2 (R1) and Q6B

##### 3.2.P.5.3 Validation of Analytical Procedures (name, dosage form)

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

Reference ICH Q2 (R1) and Q6B

#### 3.2.P.5.4 Batch Analyses

Results of not less than three batch consecutive analyses (including the date of manufacture, place of manufacture, batch size and use of batch tested) must be presented. The batch analysis must include the results obtained for all specifications at release.

**Reference ICH Guidelines: Q3B, Q3C, Q6A, and Q6B**

#### 3.2.P.5.5 Characterisation of Impurities (name, dosage form)

Information on the characterization of impurities should be provided, if not previously provided in “3.2.S.3.2 Impurities”.

**Reference ICH Guidelines: Q3B, Q5C, Q6A, and Q6B**

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

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

Reference ICH Guidelines: Q3B, Q6A, and Q6B

#### **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”.

Refer to ICH Guidelines: Q6A and Q6B

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

A description of the container closure system 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.

The suitability of the container closure system used for the storage, transportation (shipping) and use of the FPP should be discussed and located in 3.2.P.2.

Refer to WHO Technical Report Series, No. 902 – Annex 9. Officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.

#### **3.2. P.8 Stability (name, dosage form)**

The purpose of stability testing is to provide evidence of how the quality of an API or FPP varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. The stability programme also includes the study of product related factors that influence its quality, for example, interaction of API with excipients, container-closure systems and packaging materials.

#### 3.2. P.8.1 Stability Summary and Conclusions (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 and shelf-life and if applicable, in –use storage conditions and shelf-life.

Refer to ICH Guidelines: Q1A, Q1B, Q3B, and Q5C, Q6A and WHO Technical Report Series, No. 953 – Annex 2

#### 3.2. P.8.2 Post-approval Stability Protocol and Stability Commitment (name, dosage form)

The post-approval stability protocol and stability commitment should be provided

Reference document: ICH Q1A and Q5C

#### 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 and

narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Information on characterisation of impurities is located in 3.2.P.5.5.

Refer to ICH Guidelines: Q1A, Q1B, Q2(R1) and Q5C

### **3.2. A APPENDICES (NAME, DOSAGE FORM)**

### **3.2. R REGIONAL INFORMATION (NAME, DOSAGE FORM)**

### **3.3 LITERATURE REFERENCES (NAME, DOSAGE FORM)**

Key literature referenced should be provided, if applicable.

## **MODULE 4: NON-CLINICAL SUMMARIES**

This module is not normally needed for multisource (generic) pharmaceutical products. It deals with the toxicity testing intended to justify the stability and safety of the product. The module is included for completeness to indicate the appropriate format and placement of the nonclinical data.

Refer to ICH M4S (R2) for additional detail on the organization of Module 4 and for ICH references on study design and data content.

### **4.1 TABLE OF CONTENTS (MODULE 4)**

### **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 toxicokinetics evaluations)

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (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
  - 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 SUMMARIES

For multisource (generic) pharmaceutical products, only Module 5.3.1 Reports of Biopharmaceutical Studies would normally be needed. However, all parts of the module are included for completeness to indicate the appropriate format and placement of the clinical data.

ICH E3 provides guidance on the organisation of clinical study reports, other clinical data, and references within a Common Technical Document (CTD).

Module 5 provides the recommended organization for the placement of clinical study reports and related information to simplify preparation and review of dossiers and to ensure completeness. The placement of a report should be determined by the primary objective of the study. Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections. An explanation such as “not applicable” or “no study conducted” should be provided when no report or information is available for a section or subsection.

Refer to ICH M4E (R2) for additional detail on the organization of Module 5 and for additional ICH references on study design and data content.

## 5.1 TABLE OF CONTENTS (MODULE 5)

A Table of Contents for study reports should be provided.

## 5.2 TABULAR LISTING OF CLINICAL STUDIES

## 5.3 CLINICAL STUDY REPORTS

### 5.3.1 Reports of Bio-pharmaceutic Studies

Bioavailability (BA) studies evaluate the rate and extent of release of the active substance from the medicinal product. Comparative BA or bioequivalence (BE) studies may use Pharmacokinetic (PK), Pharmacodynamic (PD), clinical or in vitro dissolution endpoints, and may be either single dose or multiple doses. 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.  
WHO guideline QAS/04.109 Rev1

#### **5.3.1.1 Bioavailability (BA) Study Reports**

BA studies in this section should include

- 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.

#### **5.3.1.2 Comparative Bioavailability (BA) and Bioequivalence (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 this section. 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 CTD.

#### **5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies**

Bioanalytical and/or analytical methods for biopharmaceutical 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**

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

### **5.3.3 Reports of Human Pharmacokinetic Studies**

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

### **5.3.4 Reports of Human Pharmacodynamic Studies**

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

### **5.3.5 Reports of Efficacy and Safety Studies**

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

5.3.5.2 Study Reports of Uncontrolled Clinical Studies References

5.3.5.3 Reports of Analyses of Data from more than one study, including any formal integrated analyses, meta-analyses, and bridging analyses

5.3.5.4 Other Clinical Study Reports

### **5.3.6 Reports of Post-marketing Experience**

For products that are currently marketed, reports that summarize marketing experience (including all signi-

ficant safety observations) should be included.

### **5.3.7 Case Report Forms and Individual Patient Listings (when submitted)**

Case report forms and individual patient data listings that are described as appendices in the ICH or WHO clinical study report guideline should be placed in this section when submitted in the same order as the clinical study reports and indexed by study.

## **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 on request.

## **REFERENCES:**

### **ICH Common Technical Document References (<http://www.ich.org>)**

1. ICH M4 - Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use (2016)
2. ICH M4E(R2) - Common Technical Document for the Registration of Pharmaceuticals for Human Use: Efficacy (2016)
3. ICH M4Q(R1) - Common Technical Document for the Registration of Pharmaceuticals for Human Use: Quality (2002)
4. ICH M4S(R2) - Common Technical Document for the Registration of Pharmaceuticals for Human Use: Safety (2002)

### **ICH Quality Guidelines**

1. ICH Q1A(R2) - Stability Testing of New Drug Substances and Products (2003)
2. ICH Q1B Stability Testing: Photostability Testing of New Drug Substances and Products (1996)
3. ICH Q1D - Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products (2002)
4. ICH Q1E - Evaluation for Stability Data (2003)
5. ICH Q2(R1) - Validation of Analytical Procedures: Text and Methodology (2005) [combines the previous Q2A and Q2B Guidelines]
6. ICH Q3A(R2) - Impurities in New Drug Substances (2006)
7. ICH Q3B(R2) - Impurities in New Drug Products (2206)
8. ICH Q3C(R6) - Impurities: Guideline For Residual Solvents Q3C(2016)
9. ICH Q5A, Q5B, Q5C, Q5D Quality of Biological Products [not needed for multisource (generic) pharmaceutical products]
10. ICH Q6A - Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (1999)
11. ICH Q6B Specifications: Test Procedures and Acceptance Criteria for Biotechnological/Biological Products (1999) [not needed for multisource (generic) pharmaceutical products]

## World Health Organization Guidelines

1. Guidelines on packaging for pharmaceutical products In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902), Annex 9
2. Stability testing of active pharmaceutical ingredients and finished pharmaceutical products In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report. Geneva, World Health Organization, 2009 (WHO Technical Report Series, No. 953), Annex 2. [Together with 2015 update table Stability Conditions for WHO Member States by Region]
3. Guideline on submission of documentation for a multisource (generic) finished pharmaceutical product (FPP): quality part, In WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-third report. Geneva, World Health Organization, 2012 (WHO Technical Report Series, No. 970), Annex 4
4. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability, In WHO Expert Committee on Specifications for Pharmaceutical Preparations: Forty-ninth report. . World Health Organization, 2015 (WHO Technical Report Series, No. 992), Annex 7.
5. Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products In WHO Expert Committee on Specifications for Pharmaceutical Preparations: Forty-ninth report. World Health Organization, (WHO Technical Report Series, No. 992), Annex 8 2015
6. Guidance for organizations performing in vivo bioequivalence studies (revision), In WHO Expert Committee on Specifications for Pharmaceutical Preparations: Fiftieth report.
7. WHO Technical Report Series, No. 996, Annex 9, 2016

## World Health Organization Templates

[<https://extranet.who.int/prequal/content/who-medicines-prequalification-guidance>]

### Quality Templates

1. Quality overall summary - product dossier (QOS-PD) (2016)
2. Quality information summary (QIS) (2016)
3. Quality information summary (QIS) of the finished pharmaceutical product (FPP) approved by the reference SRA (QIS-SRA) (2013)

### Bioequivalence Template

1. Presentation of bioequivalence trial information form (BTIF) (2017)
2. Make reference to guideline for bioavailability and bioequivalence studies in
3. ECOWAS region, (2012), 4.5b page 32 and the WHO Template on Bio waiver ]

### Labelling Templates

1. Patient information leaflet – Template  
Annotated Patient information leaflet template (2016)  
Section Guidance for Part 3 Patient information Leaflet for WHOPAR 2016

2. Summary Product Characteristics (SmPC) Template (2016)  
Annotated Summary Product Characteristics (SmPC) Template (2016)  
Section Guidance for Part 4 Summary Product Characteristics (SmPC) for WHOPAR 2016
3. Annotated Labelling Template (2016)  
Section Guidance for Part 5 Labelling for a WHOPAR 2016

## **ANNEX A: PRODUCT LABELLING GUIDANCE**

There are three official languages in the ECOWAS region. These are English, French and Portuguese. Applications for products seeking a region-wide market authorization shall be submitted in English. However, the summary product characteristics, labelling and packaging information shall be submitted in all the three official languages of the region (English, French and Portuguese).

Where applicants wish to register the product in a specific country, the official language of that country SHALL be used for the application, the technical package and the product labelling. In cases where there is the need to translate a document from its original language into the other languages used in the region, the accuracy of the translations is the responsibility of the applicant. For applications originating outside the ECOWAS region the translations shall be authenticated by the nearest Embassy of an ECOWAS member state.

The Guidance and templates for product labelling shall be based on the ECOWAS guidance or the current WHO Guidance documents for the Package Leaflet, Summary of Product Characteristics and Labelling which is available from the WHO website at <https://extranet.who.int/prequal/content/contents-and-structure-whopar>.

### **MODULE 1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS (SMPC)**

The format of the SmPC document is to be consistent with the WHO SmPC template. The information is given in the official language of the ECOWAS Member State giving market authorization.  
Refer to WHO SmPC Guidance and Annotated Template  
Use WHO SmPC Template

### **MODULE 1.3.2 PATIENT INFORMATION LEAFLET**

The format of the PIL is to be consistent with the WHO PIL template. The information is given in the official language of the ECOWAS Member State giving market authorization.  
Refer to WHO PIL Guidance and Annotated Template  
Use WHO PIL Template

### **MODULE 1.3.3 CONTAINER LABELLING (INNER AND OUTER LABELS)**

The primary and secondary packaging must include the following information in a legible, understandable and indelible manner. The information is given in the official language of the ECOWAS Member State giving market authorization.  
The Container Labelling is to be consistent with the WHO template.  
Refer to WHO Guidance  
Use WHO Annotated Template

## **ANNEX B: FORMS**

### **B.1 MODEL COVER LETTER LINK**

Refer to Model Cover Letter in separate document

### **B.2 MODEL APPLICATION FORM FOR DRUG MARKET AUTHORIZATION**

Refer to Model Application Form in separate document

### **B.3 MODEL LETTERS OF ACCESS**

Include this in Module 1 – Administration and Product Information, submodule 1.2.5 of the application in CTD format

Refer to Model letter of Access to the CEP in separate document

Refer to Model letter of Access to the APIMF in separate document

## B.4 MODEL FEE FORM

### Application for Market Authorization Fee Form

Form to be inserted in Module 1.2.2 of the Common Technical Document

#### 1. IDENTIFICATION (“refer to table 1.1 on page 45”)

Product Name	
as per Drug Submission Application form (item 6):	
Name of manufacturer	
(Full legal name - no abbreviations)	
as per Drug Submission Application form (item 10):	
Address of manufacturer	
as per Drug Submission Application form (items 11-31):	
Telephone Number:	Fax Number:
Contact Person:	E-mail:
Name/address of company (billing contact) to whom invoice	
is to be sent (if different from manufacturer):	
Telephone Number:	Fax Number:
Contact Person:	E-mail:

<b>Official use only</b>
Invoice Number _____
Amount paid .....
Date of payment .....
Name and address of Bank .....
Cheque Number _____
Application Number _____
Screened by _____

## 1. 2. FEES FOR THE REVIEW OF APPLICATIONS FOR MARKETING AUTHORIZATION

Check the appropriate box to indicate the applicable submission, supplement or application fee.

#	Application Class	Description	Fee (\$USD)	•Check one
1	Registration of a Pharmaceutical Product		\$	
1a.	Fully Manufactured in ECOWAS		\$	
1b.	Imported into ECOWAS		\$	
2	Renewal of Registration		\$	
2a.	Fully manufactured in ECOWAS		\$	
2b.	Imported into ECOWAS		\$	
3.	Variation of Registration		\$	
3a.	Major variation		\$	
3b.	Minor variation		\$	

\* Other fees including those for appeal, replacement of certificates, laboratory tests among others may be charged by various country MRAs as their legislation requires.

## 3. METHOD OF PAYMENT

Applications, whether submitted to WAHO or to NMRA shall be accompanied by the appropriate application fees.

Application fees shall be paid for each application submitted. This shall be in the form of a Bankers' draft or by wire transfer to the account to be designated by the applicable NMRA or WAHO.

- International bank draft
- Wire (include bank confirmation)

## ANNEX C: TEMPLATES

Refer to World Health Organization Templates found at [\[https://extranet.who.int/prequal/content/who-medicines-prequalification-guidance\]](https://extranet.who.int/prequal/content/who-medicines-prequalification-guidance)

### C.1 Module 2 Quality Overall Summary – product dossier (QOS-PD)

### C.2 Module 2 Quality information Summary (QIS)

Quality information summary (QIS) of the finished pharmaceutical product (FPP) approved by the reference SRA (QIS-SRA)

### C.3 Module 1.4.1 Presentation of Bioequivalence Trial Information Form (BTIF)

Request for a Bio waiver template (to be determined)



## **ANNEX D: GUIDANCE DOCUMENTS**

## **ANNEX E: MANAGEMENT OF APPLICATIONS AND STANDARD OPERATING PROCEDURES**

For pharmaceutical products that have been evaluated by a stringent drug regulatory authority, and also those that have been prequalified by the World Health Organization, an abridged file abstract will be required.

As for other products, including those for specific or neglected tropical diseases, a complete file will be required.

### **1.4 GENERAL POLICIES ON APPLICATIONS**

A separate application is required for each product. For purposes of clarification, one application could be submitted for products containing the same active ingredients and the same strength made by the same manufacturer at the same manufacturing site, to the same specifications and dosage form, but differing only in packing or pack sizes. On the other hand, separate applications shall be submitted for products that contain the same active ingredient(s) but of different salts, different strength, dosage form and proprietary or brand name.

#### **1.4.1 Classes of Applications**

Applications shall be classified into three (3)

- New Applications
- Renewal of applications (i.e., registration)
- Variation of Applications (i.e., of a registered product)

#### **1.4.2 New Applications**

Applications for the registration of a pharmaceutical product either submitted to the Director General of WAHO for the granting of region wide market authorization or submitted to a particular NMRA in the region for the very first time shall be considered a new application. In addition to the dossier submitted, the applicant shall provide:

- i. Samples of the product in the commercial pack(s) from one batch with batch certificates of analysis per the samples schedule defined by WAHO (check [www.wahooas.org](http://www.wahooas.org)) or the NMRA.
- ii. Certificate of Pharmaceutical Product issued in accordance with the format approved by the WHO and issued by the competent drug regulatory authority of the country of Origin/ Manufacture (submitted in Module 1 of the PD).
- iii. A site master file of the plant in which the product was manufactured. (submitted in Module 3)
- iv. For NCEs and innovator products the pharmacovigilance plan shall be submitted. (submitted in Module 1.2.8 (PSURs))

#### **1.4.3 Applications for Renewal of Registration**

Applications for renewal of registration shall be made at least 3 months before the expiry of existing registration by submitting the following:

- i. Fully filled application form for renewal of registration
- ii. Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.
- iii. Periodic Safety Update Reports (PSUR)
- iv. Proof of interchangeability for multisource (generics) as explained in Part 5.
- v. Any other requirements that WAHO or the NMRA may determine
- vi. Samples of the product in the commercial pack(s) from one batch with batch certificates of analysis per the samples schedule defined by WAHO or the NMRA.
- vii. A site master file of the plant in which the product was manufactured.

#### 1.4.4 Application for Variation of a registered product

Applications for variation to a registered product shall be made according to requirements stipulated below:

- i. Dully filled application form for variation of registration
- ii. Samples of the product reflecting the variation
- iii. A site Master File of the manufacturer (if the variation is or includes a change in the name, site and/or address of the manufacturer).
- iv. Other documents to support or justify the variation.

### 1.5 SUBMISSION OF APPLICATION

Applications for the registration of products for which a region wide market authorization is being sought shall be made to the Director General of WAHO through the identified Coordinating NMRA indicated in the Expression of Interest (EOI) in accordance with the approved format. For products meant for marketing authorization in a specific country, the application shall be sent to the Head of the NMRA in that country.

### 1.6 APPLICATION FEES

Application fees shall be paid for each application submitted.-This shall be in the form of a Bankers' draft or by wire transfer to the account to be designated by the applicable NMRA or WAHO. Refer to the fee form in Annex B.

#### 1.6.1 Application fee for registration of a pharmaceutical product:

Imported in to ECOWAS	US\$
Fully manufactured in ECOWAS	US\$

#### 1.6.2 Application fee for renewal of registration of a pharmaceutical product:

Imported into ECOWAS	US\$
Fully manufactured in ECOWAS	US\$
Application fees for variation of Registration	US\$

Other fees including those for appeal, replacement of certificates, laboratory tests among others may be charged by various country MRAs as their legislation requires.

### 1.7 RECEIPT AND EVALUATION OF DOSSIERS

Applications, whether submitted to WAHO or to NMRAs shall be accompanied by the appropriate application fees.

#### 1.7.1 Evaluation process

WAHO and NMRAs will assign application numbers serially to applications received and evaluate them on a first in first out (FIFO) basis. Preference and priority will be given to products for priority public health diseases such as Malaria, HIV/AIDS, Tuberculosis, and other neglected tropical diseases. Special consideration will be given to products manufactured by companies operating in member countries of the ECOWAS region. A committee of experts will be constituted at the WAHO secretariat made of regulatory officials and other scientists from member countries. Where necessary, specialists will be consulted for professional opinion on various sections of the dossiers. At country level evaluation will be done by in country evaluators using this guideline and Standard Operating Procedures for evaluation of dossiers, Additional information may be requested for during evaluation and if no response is received within six months of the request, the application will be discontinued. For applications made to WAHO, laboratory analysis based on the validated in-house or pharmacopoeia methods submitted by applicants shall be performed in accordance with approved SOP in accredited quality control laboratories.

For purposes of verification of compliance to cGMP, all applications shall be accompanied by a Site Master

File. An inspection may be conducted by WAHO or the NMRA of the country in which marketing authorization is being sought. Report and recommendations of WAHO inspection teams shall be shared with NMRAs to avoid duplication. Decisions on registration shall be based on the dossier evaluation report, quality control report and inspection report on compliance to cGMP.

## **1.8 TIMELINES**

Complete applications for expedited registration (Locally manufactured and Priority Medicines only), Post Approval Variation and Renewal of registration will be processed within 90 working days of receiving the applications. Complete new applications will be processed within 12 months of receipt of the application. The applicant will be required to provide any requested additional data within 6 months. In case additional time is required, a formal request must be submitted.

## **1.9 WITHDRAWAL OF AN APPLICATION**

When the applicant fails to submit written responses to queries within 6 months from the date of their issuance, it will be deemed that the applicant has withdrawn the application or if the queries have been reissued for a second time and the applicant provides unsatisfactory responses, the product will be disqualified and the application will be rejected. The applicant will be required to apply afresh.

## **1.10 VALIDITY OF REGISTRATION**

The registration of a pharmaceutical product at WAHO or by country NMRA shall be valid for five (5) years unless otherwise suspended or revoked by the NMRA, or withdrawn by applicant.

## **1.11 APPEALS**

Any person aggrieved by a decision in relation to any application for marketing authorization of a pharmaceutical product may within two (2) months from the date of notice of the decision, make representations in writing to WAHO or the appropriate NMRA and submit additional data to support the appeal.

Documentation in support of the manufacturer's request to appeal a regulatory decision is placed in Module 1.1.

## ANNEX XX – SAMPLE COVER LETTER

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

<Applicant's reference>

<Date>

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

Dear Sir/Madam,

**Subject: 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 <the ECOWAS Region> or <the following ECOWAS member countries .....> 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., NMRA's control 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 anti-virus 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>

**MODEL APPLICATION FORM  
FOR DRUG MARKET AUTHORIZATION (ENG)**

Submit 2 months in advance of the application dossier. Include this form in Section 1.2.1 of the CTD.

**MODULE 1.2.1 – APPLICATION FORM**

NMRA use only  
 Application No. \_\_\_\_\_ Date of Receipt (YYYY-MM-DD) \_\_\_\_\_  
 Number of Volumes/CDs Received \_\_\_\_ Number of Samples Received \_\_\_\_  
 Fees Paid – YES/NO  
 Name of NMRA person who received the document \_\_\_\_\_

**PART 1: APPLICATION INFORMATION**

	New product
	Renewal of a market authorization
	Reintroduction of a deleted Market Authorization (MA)
	Variation of a market authorized product

**Proposed area of marketing**

- ECOWAS Region
- Selected ECOWAS Member State(s) (Please identify)

Number of volumes **sent** .....

Number of CDs **sent** .....

**CHARACTERISTICS OF SAMPLES ENCLOSED**

Number of samples .....

Expiry date.....

Lot /batch Numbers .....

Lot/batch certificate of analysis number:.....

**PART 2: APPLICANT INFORMATION**

**A. Name and address of Applicant**

Name of Company .....

(Complete legal name – do not use abbreviations)

Head office address: .....

Web site: .....

Email:.....

**B. Person in the country/ECOWAS authorized to represent the applicant for THIS application**

Name ..... Title.....

Name of Company if applicable .....

(Complete legal name – do not use abbreviations)

Address .....

Tel..... Fax.....

e-mail.....

**PART 3: PRODUCT INFORMATION:** (applicant completes this)

1. Brand Name, Trade Name or Product Name  
(the name as it appears on the product label) .....
2. International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API)  
.....
3. Strength of Active Pharmaceutical Ingredient (API) per unit dosage form:

**PART 4 – PRODUCT FORMULATION INFORMATION**

Pharmaceutical Dosage Form	
Route(s) of Administration	
Pharmaceutical Group	
ATC Code	
Proposed Indication/Use	

**Proposed Distribution Category**

<input type="checkbox"/>	Controlled Substance
<input type="checkbox"/>	Prescription only Medicine (POM)
<input type="checkbox"/>	Pharmacy Medicine
<input type="checkbox"/>	Over the Counter Medicine
<input type="checkbox"/>	*

Container Type	
Package Size	
Visual description of the medicine	
Proposed Storage conditions	
Proposed Storage conditions after first opening	
Proposed Shelf Life	..... months at °C
Proposed Shelf Life after first opening	..... Hours/days/Weeks at °C
Proposed Shelf Life after reconstitution or dilution	..... Hours/days/Weeks at °C

**Medicinal (Active Ingredient(s)) and Excipients**

CAS No. (if applicable)	Ingredient Name	Standard*	Strength	Units	Per	Calculated as Base?	
						↑Yes	↑No
						↑Yes	↑No
						↑Yes	↑No
						↑Yes	↑No
<b>Name Excipients</b>							

*\*State the reference/monograph **standard** such as British Pharmacopeia (BP), United States Pharmacopeia (USP), Ph. Eur, Japanese Pharmacopeia, In-house monograph (Mfr Std) etc. used for Finished Medicinal Product*

## PART 5: NATIONAL, REGIONAL AND INTERNATIONAL STATUS OF THE PRODUCT

For each country category indicate the status of an application or marketing status of the product. Include the Certificates of Pharmaceutical Product and other appropriate documentation in Module 1.2.7 of the CTD.

- Country of Origin
- Countries with Stringent Regulatory Authorities
- Other African Regions
- ECOWAS Member States
- Other

<b>Authorized</b> Country: Date Proprietary Name of Product: Authorization Number:	
<b>Market Application in progress</b> Country: Date Submitted: Proprietary Name of Product:	<b>Withdrawn (by applicant after Authorization)</b> Country: Date Proprietary Name of Product: Reason:
<b>Rejected</b> Country: Date Proprietary Name of Product: Reason	<b>Suspended/revoked/stop sale (by NMRA)</b> Country: Date Proprietary Name of Product: Reason:

### WHO PREQUALIFIED APIs AND FINISHED PRODUCTS

Are the APIs prequalified by the WHO?

- NO  
 YES (provide evidence in Module 1.2.7 of the CTD)

Is the finished product prequalified by the WHO?

- NO  
 YES (provide evidence in Module 1.2.7 of the CTD)

### API with a CEP

- NO  
 YES (provide evidence in Module 1.2.7 of the CTD)

### PART 6 : PRICE (where applicable)

Wholesale price (taxes excluded).....  
 Treatment price.....  
 Public price.....



**PART 7 : DECLARATION BY APPLICANT**

I, the undersigned, certify that the information and material included in this drug application are accurate and complete.

Name of Authorized Official	Signature	Date		
		YYYY	MM	DD
Title	Telephone No.	Fax No.		
	Email address			
Name of Company to which the Authorized Official Belongs				

If the authorized official is a third party acting on behalf of the applicant identified in Part 2, a letter of authorization, signed by the applicant, must be filed with the completed application form.

## SAMPLE LETTER OF ACCESS TO CEP

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

<Applicant>

<Address>

<Address>

<Post code> <Town>

<Country>

<Applicant's reference>

<Date>

<National Medicines Regulatory Authority>

<Address>

<Address>

<Post code> <Town>

<Country>

Dear Sir/Madam,

Subject: Authorization to access Certificate of Suitability (CEP)

Reference is made to the above subject matter.

Consent is hereby granted to <NMRA> 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 <ECOWAS or member country> before written approval is granted by the NMRA.

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

Any questions arising from the < NMRA's> evaluation of this CEP should be forwarded to:

(Name and address)

Yours faithfully

{Signature of Company Representative}

{Name}

{Position in Company}

{Date}

## ANNEX V: LETTER OF ACCESS TO ECOWAS APIMF

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

<Applicant's reference>

<Date>

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

Dear Sir/Madam,

Subject: Authorization to access Active Pharmaceutical Ingredient Master File

Reference is made to the above subject matter.

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

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

(Name of company or individual)

The substance is manufactured by:

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

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

A formal agreement exists between the applicant of the medicine and the manufacturer of the API, which ensures that information will be communicated between them and to ECOWAS-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 ECOWAS 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 ECOWAS before written approval is granted by the NMRA.

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

This APIMF (or data identical to that contained therein) has also been submitted to and approved by the regulatory authorities in (list of countries with stringent regulatory systems), and the [name(s) of ECOWAS

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

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

{Name and address}

Yours faithfully

{Signature of Company Representative}

{Name}

{Position in Company}

{Date}

**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:**

<b>Non-proprietary name(s) of the finished pharmaceutical product(s) (FPP)</b>			
<b>Proprietary name(s) of the finished pharmaceutical product(s) (FPP)</b>			
<b>International non-proprietary name(s) of the active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, polymorph)</b>			
<b>Applicant name and address</b>			
<b>Dosage form</b>			
<b>Reference Number(s)</b>			
<b>Strength(s)</b>			
<b>Route of administration</b>			
<b>Proposed indication(s)</b>			
<b>Contact person responsible for this application</b>	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:	
<input type="checkbox"/>	Confirmation of API Prequalification document: <ul style="list-style-type: none"><li>a copy of the confirmation of API Prequalification document should be provided in <i>Module 1</i>, and</li><li>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).</li></ul>
<input type="checkbox"/>	Certificate of suitability to the European Pharmacopoeia (CEP): <ul style="list-style-type: none"><li>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:<ul style="list-style-type: none"><li><input type="checkbox"/> yes, <input type="checkbox"/> no;</li></ul></li><li>a copy of the most current CEP (with annexes) and written commitment should be provided in <i>Module 1</i>;</li><li>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</li><li>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).</li></ul>
<input type="checkbox"/>	Active pharmaceutical ingredient master file (APIMF): <ul style="list-style-type: none"><li>a copy of the letter of access should be provided in <i>Module 1</i>; and</li><li>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.</li></ul>
<input type="checkbox"/>	Active pharmaceutical ingredient pre-qualified by WHO Provide evidence from WHO
<input type="checkbox"/>	Full details in the PD: <ul style="list-style-type: none"><li>Summaries of the full information should be provided under the appropriate sections; see Section 3.2.S in the quality guideline.</li></ul>

#### 2.3.S.1 General Information (name, manufacturer)

##### 2.3.S.1.1 Nomenclature (name, manufacturer)

- (a) **(Recommended) International Non-proprietary name (INN):**
- (b) **Compendial name, if relevant:**
- (c) **Chemical name(s):**

- (d) **Company or laboratory code:**
- (e) **Other non-proprietary name(s) (e.g. national name, USAN, BAN):**
- (f) **Chemical Abstracts Service (CAS) registry number:**

**2.3.S.1.2 Structure (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, colour, physical state):**
- (b) **Solubilities:**

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 biowaiver, stability, scale-up, pilot and, if available, production scale batches:

### 2.3.S.3 Characterisation (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 centres and configurations) of the API batch(es) used in comparative bioavailability or biowaiver studies:
- (c) Summary of studies performed to identify potential polymorphic forms (including solvates): <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):

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**)		

\* 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 compendial 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		
Other		

(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							
<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:

(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 biowaiver, stability, commercial:
  - i. Summary of batch numbers:

Batch number(s) of the FPPs used in			
Bioequivalence or biowaiver	<e.g. bioequivalence batch A12345> <e.g. biowaiver batch X12345>		
For proportional strength biowaiver: the bioequivalence batch of the reference strength			
Dissolution profile studies			
<b>Stability studies (primary batches)</b>			
< packaging configuration I >			
< packaging configuration II >			
<i>&lt;Add/delete as many rows as necessary&gt;</i>			
<b>Stability studies (production batches)</b>			
< packaging configuration I >			
< packaging configuration II >			
<i>(Add/delete as many rows as necessary)</i>			
<b>Validation studies (primary batches) if available</b>			
< packaging configuration I >			
< packaging configuration II >			
<i>(Add/delete as many rows as necessary)</i>			
<b>Validation studies (at least the first three consecutive production batches) or code(s)/version(s) for process validation protocol(s)</b>			

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 biowaiver		Stability		Process validation		Commercial (2.3.P.1)	
	<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>		<Batch nos. and sizes>	
	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%	Theor. quantity per batch	%
<complete with appropriate 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 biowaiver), including strength, batch number, type of study and reference to the data (volume, page):

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

Summary of the multi-point dissolution profiles for the biobatch(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 biowaiver studies and the process described in 2.3.P.3.3:

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

- (a) Discussion of the suitability of the container closure system (described in 2.3.P.7) used for the storage, transportation (shipping) and use of the 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 compendial 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 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:



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

### 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:

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

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

<b>Test</b>	<b>Acceptance criteria</b>	<b>Results</b>		
		<b>&lt;batch x&gt;</b>	<b>&lt;batch y&gt;</b>	<b>etc.</b>
Description				
Identification				

Test	Acceptance criteria	Results		
		<batch x>	<batch y>	etc.
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 Characterisation of Impurities

- (a) Identification of potential and actual impurities:

Degradation product (code name, chemical name and compendial 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: Test	<x mg/day>	
	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

biowaiver):

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

iii. Justification of proposed acceptance criteria for impurities:

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

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

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

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

#### 2.3.P.7 Container Closure System

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

Description (including materials 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

Parameter	Details	
	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	<i>&lt;at least one production batch per year (unless none is produced that year) in each container closure system &gt;</i>	
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

#### **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: Not 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:** Not applicable.

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

- (a) **Summary of the details of manufacture, characterization and controls, with cross references to supporting safety data (nonclinical and/or clinical) for the novel excipients:** Not applicable. Novel excipients are not accepted in 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 biowaiver batches):**

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

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

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

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES			
<b>ATTACHMENT NUMBER:</b>			
<b>HPLC Method Summary</b>		<b>Volume/Page:</b>	
<b>Method name:</b>			
<b>Method code:</b>		<b>Version and/or Date:</b>	
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):			



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

## QUALITY INFORMATION SUMMARY (QIS)

### <Dossier reference number: e.g. HA999>

### FOREWORD

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

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

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

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

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

## 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 <sup>1</sup>	Title: First name: Family Name:
Contact person's job title	
<b>Contact person's postal address</b>	
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	

**(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:	
<input type="checkbox"/>	Confirmation of API prequalification document
<input type="checkbox"/>	Certificate of suitability to the European Pharmacopoeia (CEP)
<input type="checkbox"/>	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: _____.
<input type="checkbox"/>	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, exhibit) batches including comparative bioavailability or biowaiver, stability, commercial:

(i) Summary of batch numbers:

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

**Summary of formulations and discussion of any differences:**

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

**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

**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 QIS>

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

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

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

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

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

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

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

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

#### 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.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.)

## 2.3.P.8 Stability

## 2.3.P.8.1 Stability Summary and Conclusions

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

Container closure system	Storage statement	Shelf-life

## 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

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

## WRITTEN COMMITMENTS OF THE MANUFACTURER – FOR WHO USE

Important note: The product information is an essential part of the medicinal product. The SmPC and PIL published with the WHOPAR have been quality assured by WHO experts and reflect the situation at the time of publication of the WHOPAR. These texts, i.e. the SmPC and the PIL are prequalified and should be adhered to. Generally, a deviation from the prequalified product information (especially as to contents) means the product can no longer be considered to be prequalified.

### API

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

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

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

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

Since stability data on three production scale batches were not provided with the application, the remaining

number of production scale batches should be put on long-term stability testing. Any significant changes or out-of-specification results should be reported immediately to WHO. The approved stability protocol should be used for commitment batches.

#### **API option 2 – CEP**

The Applicant provided a commitment in writing (date of letter of commitment) to inform WHO in the event that the CEP is revised or withdrawn, and that revisions to the CEP will be handled as per variation 5 (Annex 5, TRS 981). Note that revisions or withdrawal will require additional consideration of the API data requirements to support the dossier.

#### **API option 3 – full details in the PD (ongoing stability study commitment)**

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

#### **FPP**

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

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

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

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

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

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

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

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

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

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

Validation data on production scale batches of not less than three (3) consecutive batches of <FPP reference number, trade name (INN of API), strength, pharmaceutical form, primary packing material> was not provided

with the application. Therefore, the Applicant submitted a written commitment (date of letter of commitment) that three consecutive production batches would be prospectively validated and a validation report—in accordance with the details of the validation protocol provided in the dossier— would be made available as soon as possible for evaluation by assessors or for verification by the WHO inspection team.

### **Change History**

#### ***Date of preparation of original QIS:***

Date of revised version	Section (e.g. S.2.1)	Revision

## PRESENTATION OF BIOEQUIVALENCE TRIAL INFORMATION

### BIOEQUIVALENCE TRIAL INFORMATION

#### **General Instructions:**

*Please review all the instructions thoroughly and carefully prior to completing the bioequivalence trial information form (BTIF). Neither the format nor the content of the document (text and tables) should be changed, except for setting horizontal page layout in subsections including wide tables.*

*Provide as much detailed, accurate and final information as possible. Note that the greyed areas are NOT to be completed in by the applicant but are for WHO use only.*

*Please state the exact location (Annex number) of appended documents in the relevant sections of the BTIF. For example, in **section 3.4.3.1** under **point b**, indicate in which Annex (number) the Certificate of Analysis can be found. This procedure must be followed throughout the entire document where location of annexed documents is requested. Please ensure that the electronic submission has the same file structure and naming as the one employed to state the location of the documents and to include annexes of the BTIF as separate files.*

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

*Should you have any questions regarding this Form, please contact the WHO Prequalification Team - Medicines.*

A properly filled out and signed original copy of the BTIF with all its annexes (including a copy on CD ROM) must be submitted to the Prequalification of Medicines Programme together with the bioequivalence part of the dossier to the address below once the dossier has been accepted for assessment and the dossier has been allocated a WHO reference number. Note however a softcopy of the BTIF should be included already in the initial dossier submission to Geneva (please see Step 1 and Step 2 of the submission procedure [http://www.who.int/prequal/info\\_applicants/info\\_for\\_applicants\\_dossier\\_SMF.htm](http://www.who.int/prequal/info_applicants/info_for_applicants_dossier_SMF.htm))

CONFIDENTIAL

Attention: WHO Prequalification of Medicines Programme

Product Name:

UNICEF Supply Division

Oceanvej 10 - 12

2100 Copenhagen Ø

Denmark

## 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) <sup>1</sup>					
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 (%)
<b>Total</b>					
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
  
- 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) Study site normal values  
*(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)*
- d) Report any results that were outside of study site normal values  
*(State location in submission of the summary of anomalous values)*

### 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

**2.5 Comments from review of Section 2 – WHO use only****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  $\pm$  SD of subjects
- e) Range and mean height and weight  $\pm$  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 – WHO 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 – WHO 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 – WHO use only

## 6 EFFICACY EVALUATION

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

Parameter	Test			Reference		
	Arithmetic mean	Standard deviation	Interindividual coefficient of variation (%)	Arithmetic mean	Standard deviation	Interindividual coefficient of variation (%)
AUC <sub>0-t</sub> (units)						
AUC <sub>0-inf</sub> (units)						
C <sub>max</sub> (units)						
t <sub>max</sub> (units)						
t <sub>1/2</sub> (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 (%)
AUC <sub>0-t</sub> (units)						
AUC <sub>0-inf</sub> (units)						
C <sub>max</sub> (units)						

- h) Comparison of the results

## 6.4 Discussion of results

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

## 6.5 Comments from review of Section 6 – WHO 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 – WHO use only

## 3 BIOANALYTICAL STUDY REPORT

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

### 3.1 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)

#### 3.1.1 Analytical protocol

(State the location of the analytical protocol)

#### 3.1.2 Identify any deviations from protocol

#### 3.1.3 Dates of subject sample analysis

#### 3.1.4 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)

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

## 8.2 Standard curves

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

- a) List number and concentration of calibration standards used
- b) State number of curves run during the study (*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 – WHO 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 – WHO use only**

**10.0 CONCLUSIONS AND RECOMMENDATIONS – WHO use only**

