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TANZANIA FOOD AND DRUGS AUTHORITY

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF HUMAN PHARMACEUTICAL PRODUCTS

(Made under Section 52 (1) of the Tanzania Food, Drugs and Cosmetics Act, 2003)

First Edition

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Foreword

The Tanzania Food and Drugs Authority (TFDA) was established under the Tanzania Food, Drugs and Cosmetics Act, Cap 219 with the mission of protecting and promoting public health by ensuring quality, safety and effectiveness of food, drugs, cosmetics and medical devices. The first step towards achieving this goal is to conduct pre-marketing evaluation of products so as to ensure that they meet standards of quality, safety and effectiveness before the products are allowed into the market. This is a fundamental requirement for authorisation of medicinal products in Tanzania.

In fulfilment of its mission, TFDA is duty-bound to ensure that data submitted as evidence of quality, safety and efficacy is solid, credible and submitted in manner that is logical and consistent. Therefore, these guidelines have been adopted from Compendium of Harmonized Common Technical Documents and Guidelines for Registration of Pharmaceutics in the East African Community. The guidelines provide guidance to applicants in the preparation of product dossier using common technical document for marketing authorization of human pharmaceutical products in Tanzania.

Through the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) process, considerable harmonization has been achieved on the organization for the modules of the registration documents with the issuance of the Common Technical Document (CTD). This format has become widely accepted by the East African Community's National Medicines Regulatory Authorities (EAC-NMRAs) and other regions.

The guidelines provide requirements on the quality, safety and efficacy information for active pharmaceutical ingredients (APIs) and finished pharmaceutical products (FPPs) that should be submitted to TFDA to support product dossier. Alternative approaches to the principles and practices described in this document may be acceptable provided that they are supported by adequate scientific justification. It is also important to note that the TFDA may request information or material, or define conditions not specifically described in these guidelines, in order to adequately assess the quality, safety and efficacy of a pharmaceutical product.

Therefore, adherence to the guidelines will ensure that all relevant information is provided in registration dossiers submitted for marketing authorization. This will facilitate efficient and effective evaluation as well as approval process. It will also help to avoid queries which results in unnecessary delays in giving approvals to new medicines thereby improving access to medicines of proven quality, safety and efficacy in the shortest possible time.

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Director General
Tanzania Food and Drugs Authority

Preface

The "*Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products' First Edition, January 2015" is* the TFDA publication which sets out procedures and requirements for the implementation of Pharmaceutical Products Registration through Common Technical Document (CTD). The CTD has five Modules:

Module 1: Administrative Requirements;

Module 2: The Quality Overall Summaries (QOS),

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

Module 4: Pre-Clinical data Requirements,

Module 5: Clinical data Requirements.

The general objective of the Common Technical Document (CTD) guidelines is to provide internationally harmonized pharmaceutics registration procedures using CTD in order to improve access to essential pharmaceutics for prevention and treatment of priority disease conditions in Tanzania.

Adherence to the guidelines by the manufacturers/applicants will facilitate timely assessments and approvals of medicinal product dossiers by the regulatory authorities for pre-marketing evaluation, marketing authorization/registration and post-marketing review.

I wish to express my gratitude to all individuals from EAC Partner States' NMRAs, regional and international organizations and EAC Secretariat and members of the Technical Working Group (TWG) on Medicines Evaluation and Registration (MER) of the East African Community Medicine Regulatory Harmonization (EAC MRH) Project who actively participated in the development of the guidelines.

Special thanks are also extended to TFDA staff and esteemed stakeholders; the dealers in pharmaceutical industry and the academia in particular members of the Tanzania Pharmaceutical Manufacturers Association (TPMA) and the Tanzania Association of Pharmaceutical Industries (TAPI) who discussed the draft guidelines and gave commendable inputs for improving the guidelines.

Mitangu Adam Fimbo
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Abbreviations and acronyms

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
CEP	Certificate of Suitability to the monograph of European Pharmacopeia
CTD	Common Technical Document
EAC	East African Community
EAC-MRH	East African Community Medicines Registration Harmonization
EAC-NMRAs	East African Community Partner States' National Medicines Regulatory Authorities
EDQM	European Directorate for the Quality of Medicines
EU	European Union
FPP	Finished Pharmaceutical Product
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
PD	Product Dossier
PHIS	Pharmaceutical Health Information System
PI	Product Information
SDRA	Stringent Drug Regulatory Authority
SmPC	Summary of Product Characteristics
TFDA	Tanzania Food and Drugs Authority

Glossary

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

Authority

Means Tanzania Food and Drugs Authority

Active pharmaceutical ingredient (API)

Means an active ingredient in any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

Active Pharmaceutical Ingredient (API) starting material

Means a raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API.

Marketing Authorization Holder (MAH)

Is a person resident/domicile in Tanzania who holds authorization to place a pharmaceutical product in the country and is responsible for that product.

Commitment batches

Means production batches of an API or FPP for which the stability studies are initiated or completed post-approval through a commitment made in a regulatory application.

Comparator product

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

Generic product

Means a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Existing API

Means an API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority.

Finished pharmaceutical product (FPP)

Means a finished dosage form of a pharmaceutical product, which has undergone all stages of manufacture, including packaging in its final container and labelling.

Innovator medicinal product

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

Manufacturer

Means a natural or legal person with responsibility for manufacturing of a medicinal product or active pharmaceutical ingredient. It involves operations such as production, packaging, repackaging, labelling and relabeling of pharmaceuticals.

Mock-up

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

Officially recognized pharmacopoeia (or compendium)

The official recognized pharmacopoeias are British Pharmacopoeia (BP), European Pharmacopoeia (Ph. Eur.), The International Pharmacopoeia (Ph.Int), Japanese Pharmacopoeia (JP) and United States Pharmacopeia (USP).

On-going stability study

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

Pilot-scale batch

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

Primary batch

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

Production batch

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

Specimen

Means a sample of the actual printed outer and inner packaging materials and package leaflet.

Stringent Drug Regulatory Authority (SDRA)

Means a National Medicines Regulatory Authority which is strict, precise, exact with effective and well-functioning systems.

Among others, it includes a regulatory authority which is:-

- A member of the International Conference on Harmonisation (ICH) (as specified on www.ich.org); or an ICH observer, being the European Free Trade Association (EFTA), as represented by Swiss Medic, and Health Canada (as may be updated from time to time); or

- A regulatory authority associated with an ICH member through a legally-binding, mutual recognition agreement including Australia, Iceland, Liechtenstein and Norway (as may be updated from time to time); or

- A regulatory Authority that has been agreed by the EAC Partner States to have an effective and well-functioning medicines regulation systems.

1. INTRODUCTION

1.1 Background

This guideline provides guidance for applicants preparing a Common Technical Document for the Registration of Medicines for Human Use (CTD) for product dossier submission to TFDA. The document describes how to organize applications based on the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines on the CTD.

According to the CTD format, each application is a collection of documents, grouped into 5 modules. Module 1 prescribes Administrative Information and Prescribing Information requirements, which is region specific. The Summaries, Quality, Non-clinical, and Clinical modules have been described in Modules 2 to 5, respectively. Applicants should not modify the overall organization of the CTD.

If not contained in the bulk of the documentation, any additional data should be included as addenda to the relevant part, together with additional expert comment that may be provided as a supplement to, or incorporated into, the relevant summary, overall summary or overview.

Information in these Modules should be present in relevant sections.

For application procedures refer Guidelines on Procedural Aspects for Application for Marketing Authorization of Human Pharmaceutical Products.

1.2 Scope

These guidelines will assist applicants to prepare applications to register Pharmaceutical products for human use in Tanzania. The format for applications is the Common Technical Document (CTD).

These guidelines apply to marketing authorization (MA) applications for Pharmaceutical products containing APIs of synthetic or semi-synthetic origin. Biological, biotechnological and herbal products are not covered by these guidelines.

MODULE 1: ADMINISTRATIVE INFORMATION AND PRODUCT INFORMATION

Module 1 should contain all administrative documents (for example, application forms and certifications), labelling, general correspondence and annexes (environmental assessments, antibiotic resistance and overseas evaluation reports), as needed. Documents should be organized in the order listed below. Generally, all of the documents in Module 1, other than the annexes, can be provided in a single volume. The annexes to the module should be submitted in separate volumes. Official language is English as a mandatory language for all medicines.

Products shall be evaluated on a First in First out (FIFO) basis and the timeline for review and communication to applicant shall be within 12 months.

1.1 Comprehensive table of contents for all modules

1.2 Cover letter

Applicants should include a Cover Letter (**Annex I**) with all applications. A copy of the letter should be placed at the beginning of Module 1. The cover letter shall be signed by the Market Authorization Holder.

1.3 Comprehensive table of content

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

1.4 Application form

An application to register a Pharmaceutical product for human use must be accompanied by a completed Application Form (**Annex II**). The application form should be dully filled with relevant information and attachments, dated signed and stamped appropriately.

1.5 Product Information

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

If the Summary Product Characteristics (SmPC) has not been approved from SDRA at the time the application is submitted in TFDA, a draft document may be included. The approved SmPC from SDRA should then be supplied to TFDA as they become available.

1.5.1 Prescribing information (Summary of Product Characteristics)

All prescription medicines should be accompanied by SmPC. Refer Guidelines on Format and Content of Summary of Product Characteristics for Pharmaceutical Products.

1.5.2 Container labelling

Product should be labeled as prescribed in the Guidelines on Format and Content of Labels for Pharmaceutical Products.

1.5.3 Patient information leaflet (PIL)

All Pharmaceutical preparations with potential for long-term use and self-administered injections and Over the Counter (OTC) must contain a patient information leaflet. Languages used for PIL and labelling should be clearly expressed in English and/or Kiswahili. *Refer* Guidelines on Format and Content of Patient Information Leaflet for Pharmaceutical Products.

1.5.4. Mock-ups and specimens

If the product applicant has a specimen or mock-up of the sample(s) presentation of the medicine available at the time of initial application, it should be included in Module1.5.2.

If there are multiple strengths and/or pack sizes, one representative specimen or mock-up for each will be sufficient. If batch number and expiry date are to be printed on the label during packaging, a statement to this effect should accompany the labels. If mock-ups or specimens are not available at the time of initial application, a text version may be submitted, however, mock-ups or specimens must be submitted to the TFDA, during the evaluation process and prior to finalization of the application.

1.6. Information about the experts

Experts must provide detailed reports of the documents and particulars, which constitute Modules 3, 4 and 5.

The requirement for these signed Expert Reports may be met by providing:

- The Quality Overall Summary, Non-clinical Overview / Summary and
- Clinical Overview / Summary in Module 2,
- A declaration signed by the experts in Module 1.6.
- Brief information on the educational background, training and occupational experience of the experts in Module 1.6.

Experts should additionally indicate in their declarations the extent, if any of their professional or other involvement with the applicant / dossier owner and confirm that the report has been prepared by them or if not, any assistance provided and by whom. Reports should be based on an independent assessment of the dossier and references must be provided for any additional claims not supported by the dossier. A sample Expert Declaration Form is provided as **Annex III.**

1.7. Certificates of Suitability of monographs of the European pharmacopoeia (CEP) or EAC-APIMF

If CEP is available, the finished product applicant should present copy of CEP in module 1.7.

Applicant should provide the Letter of Access to CEP (**Annex IV**) or Letter of Access to EAC APIMF (**Annex V**)**,** as appropriate from API manufacturer. These letters should be included in Module 1.7.

1.8 Good Manufacturing Practice (GMP)

For all medicines, irrespective of the country of origin, all key manufacturing and/or processing steps in the production of active pharmaceutical ingredient ingredients and finished pharmaceutical products must be performed in plants that comply with TFDA GMP guidelines. Attach a WHO-type certificate of GMP. For more information on GMP requirements and application for GMP inspection, refer TFDA Guidelines on Good Manufacturing Practice for more guidance.

If available at the time of submission of application, GMP certificates from EAC-NMRA and/or SDRA or an evidence for application for GMP inspection should be submitted in module 1.8.

1.9 Good Clinical Practice (GCP) or Good Laboratory Practice (GLP)

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

1.10 Regulatory status

1.10.1 Registration status from countries with Stringent Drug Regulatory Authorities (SDRAs)

Provide registration status of the Pharmaceutical product applied for registration in the countries with SDRAs and attach evidence(s) for the same.

1.10.2 Registration status in EAC Partner States

Provide registration status of the Pharmaceutical product applied for registration in the EAC region and attach evidence(s) for the same.

1.10.3 List of countries in which a similar application has been submitted

The applicant should provide, in Module 1.10.1 of the dossier, a list of countries in which a similar application has been submitted, dates of submission (if available) and the status of these applications. This should detail approvals (with indications) and deferrals, withdrawals and rejections with reasons in each case.

1.10.4 Statement on whether an application for the product has been previously rejected, withdrawn or repeatedly deferred in the EAC Partner States

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

1.11 Evidence of API and/or FPP prequalified by WHO

If an evidence indicating that the active pharmaceutical ingredient and/or finished pharmaceutical product are prequalified by WHO is available, it should be presented in Module 1.12

1.12 Manufacturing and Marketing authorization

Submit a Certificate of Pharmaceutical Product in format recommended by the World Health Organization together with a valid Manufacturing Authorization for pharmaceutical production. If available, evidence for prequalification of medicinal product by WHO should be submitted.

1.13 Product samples

Sufficient number of samples should be submitted together with the application. The quantity of samples should be adequate to carry out full specification analysis plus one repeat.

Batch Number, Manufacturing Date and Expiry Date should be dynamically printed on packages for all medicines except in situations where there is space is a restriction, the details can be on secondary packages with the primary pack having at least the batch number and expiry date. Pre-printing of the batch number, manufacturing date and expiry date will not be acceptable.

MODULE 2: OVERVIEW & SUMMARIES

2.1 Table of contents of Module 2

A table of contents for module 2 should be provided.

2.2 CTD Introduction

2.3 Quality Overall Summary (QOS)

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

Complete Quality Overall Summary (QOS) **Annex VI** *following the guidance below.*

2.3.S Active pharmaceutical ingredient (name, manufacturer)

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

Information from 3.2.S.1 should be included.

2.3.S.2 Manufacture (name, physical address)

Information from 3.2.S.2 should be included:
Information on the manufacturer;

- A brief description of the manufacturing process and the controls
- A flow diagram, as provided in 3.2.S.2.2;
- 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 Characterization

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

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

2.3.S.4 Control of Drug Substance

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

Specification from 3.2.S.4.1 should be provided.

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

2.3. S.5 Reference Standards or Materials

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

2.3.S.6 Container Closure System

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

2.3.S.7 Stability

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

The post-approval stability protocol, as described in 3.2.S.7.2, should be included.
A tabulated summary of the stability results from 3.2.S.7.3, with graphical representation where appropriate, should be provided.

2.3.P Finished Pharmaceutical Product (name, dosage form)

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

A discussion of the information and data from 3.2.P.2 should be presented.
A tabulated summary of the composition of the formulations used in clinical trials and a presentation of dissolution profiles should be provided, where relevant.

2.3.P.3 Manufacture (name, physical address)

Information from 3.2.P.3 should include:
Information on the manufacturer

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

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

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

2.3.P.4 Control of Excipients

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

2.3.P.5 Control of Drug Product

A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterization of impurities should be provided. *Specification(s) from 3.2.P.5.1 should be provided.*

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

2.3.P.6 Reference Standards or Materials

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

2.3.P.7 Container Closure System

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

2.3.P.8 Stability

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

Stability studies should be provided for each pack type applied for registration.

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.

2.4 Non-Clinical overview

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

The non-clinical 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

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

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

2.5. 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.

The clinical Overview should be presented in the following sequence

- Product Development Rationale
- Overview of Biopharmaceutics
- Overview of Clinical Pharmacology
- Overview of Efficacy
- Overview of Safety
- Benefits and Risks Conclusions
- Literature References

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

2.6 Nonclinical Written 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 Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Safety for guidance on the format and the content of this part.

For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

2.7 Clinical Summary

The Clinical Summary is intended to provide a detailed, factual summarization 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.

Refer ICH Guidance on the Common Technical Document for the registration of pharmaceuticals for human use: Efficacy for guidance on the content of this section.

The following order is recommended:

2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods: Generic applications

The objective of CTD Module 2.7.1 is to summarize all relevant information in the product dossier with regard to bioequivalence studies and/or comparative dissolution and associated analytical methods.

Guideline on the Therapeutic equivalence studies: Presentation of Biopharmaceutical and Bio-analytical Data contains a set of template tables to assist applicants in the preparation of Module 2.7.1 with regard to data to be presented. Furthermore, it is anticipated that a standardized presentation will facilitate the evaluation process.

Refer the Guidelines on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance.

2.7.2 Summary of Clinical Pharmacology Studies

Refer the Guidelines on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance.

2.7.3 Summary of Clinical Efficacy

Refer the Guidelines on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance.

2.7.4 Summary of Clinical Safety

Refer the Guidelines on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance.

2.7.5 Literature References

2.7.6 Synopses of Individual Studies

MODULE 3: QUALITY

3.1 Table of contents of Module 3

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

3.2 Body of data

3.2. S Active pharmaceutical ingredient (API))

The API information can be submitted to the Authority in one of the following four options:

a) Option 1: Full details in the Product Dossier (PD)
b) Option 2: Certificate of suitability of European Pharmacopeia(CEP)
c) Option 3: Active pharmaceutical ingredient pre-qualified by WHO
d) Option 4: EAC Active Pharmaceutical Ingredient Master File (EAC-APIMF)

The applicant should clearly indicate at the beginning of the API section in the Marketing Authorization (MA) application and in the QOS how the information on the API for each API manufacturer is being submitted.

Where reference is made to CEP, the finished product applicant must have written permission to access the CEP from the CEP holder. Applicant should provide the *Letter of Access to CEP,* as appropriate from API manufacturer (**Annex IV**). Letter of access should be included in Module 1.7.

Where reference is made to APIMF, the finished product applicant must have written permission to access the APIMF from the company that supplied the APIMF and must provide the APIMF file number to the Authority. Applicant should provide the *Letter of Access to* APIMF*,* as appropriate from API manufacturer (**Annex V**). Letter of access should be included in Module 1.7.

The applicant's open part of the APIMF should be included in Module 3.2.S of the Quality documentation presented in the CTD format. The API manufacturer's restricted (closed) part is supplied to Authority directly by the API manufacturer when required.

The API information submitted by the applicant/FPP manufacturer should include the following for each of the options used.

a) Option 1: Full details by completing Section 3.2.S.1 - 3.2.S.7 of these guidelines

Information on the *3.2.S Active pharmaceutical ingredient* sections, including full details of chemistry, manufacturing process, quality controls during manufacturing and process validation for the API, should be submitted in the FPP dossier as outlined in the subsequent sections of this guideline.

3.2.S.1 General information

3.2.S.1.1 Nomenclature

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

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

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

3.2.S.1.2 Structure

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

This information should be consistent with that provided in section 3.2.S.1.1. For APIs existing as salts, the molecular mass of the free base or acid should also be provided.

3.2.S.1.3 General properties

A list should be provided of physicochemical and other relevant properties of the API.

This information can be used in developing the specifications, in formulating FPPs and in the testing for release and stability purposes.

The physical and chemical properties of the API should be discussed including the physical description, solubilities in common solvents (e.g. water, alcohols, dichloromethane, acetone), quantitative aqueous pH solubility profile (e.g. pH 1.2 to 6.8, dose/solubility volume), polymorphism, pH and pKa values, UV absorption maxima and molar absorptivity, melting point, refractive index (for a liquid), hygroscopicity, partition coefficient, etc. (see table in the QOS). This list is not intended to be exhaustive, but provides an indication as to the type of information that could be included.

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

Physical description

The description should include appearance, colour and physical state. Solid forms should

be identified as being crystalline or amorphous (see 3.2.S.3.1 for further information on API solid forms).

Solubilities/quantitative aqueous pH solubility profile

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

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

The solubilities over the physiological pH range (pH 1.2 to 6.8) in several buffered media should be provided in mg/ml. If this information is not readily available (e.g. literature references), it should be generated in-house.

For solid oral dosage forms, the dose/solubility volume should be provided as determined by:

$$\textit{Dose/solubility volume} = \frac{\textit{largest dosage strength (mg)}}{\textit{the minimum concentration of the drug (mg/ml)*}}$$

* corresponding to the lowest solubility determined over the physiological pH range (pH 1.2 to 6.8) and temperature (37 ± 0.5 °C).

As per the Biopharmaceutics Classification System (BCS), *highly soluble (or highly water-soluble)* APIs are those with a dose/solubility volume of less than or equal to 250 ml.

For example, compound A has as its lowest solubility at 37 ± 0.5 °C, 1.0 mg/ml at pH 6.8 and is available in 100 mg, 200 mg and 400 mg strengths. This API would not be considered a *BCS highly soluble* API as its dose/solubility volume is greater than 250 ml (400 mg/1.0 mg/ml = 400 ml).

Polymorphism

a) The polymorphic form(s) present in the proposed API should be listed in section 3.2.S.1.3;

b) The description of manufacturing process and process controls (3.2.S.2.2) should indicate which polymorphic form is manufactured, where relevant; the literature references or studies performed to identify the potential polymorphic forms of the API, including the study results, should be provided in section 3.2.S.3.1; and if a polymorphic form is to be defined or limited (e.g. for APIs that are not *BCS highly soluble* and/or where polymorphism has been identified as an issue), details should be included in 3.2.S.4.1 through 3.2.S.4.5.

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

Particle size distribution

Studies performed to identify the particle size distribution of the API should be provided in section 3.2.S.3.1 (refer to this section of this guideline for additional information).

Information from literature

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

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s) (name, physical address)

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

The facilities involved in the manufacturing, packaging, labelling, testing and storage of the API should be listed. If certain companies are responsible only for specific steps (e.g. milling of the API) it should be clearly indicated.

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

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

3.2.S.2.2 Description of manufacturing process and process controls

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

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

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

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

The *API starting material* should be fully characterized with respect to identity and purity.

The *starting material for synthesis* defines the starting point in the manufacturing process for an API to be described in an application. The applicant should propose and justify which substances should be considered as *starting materials for synthesis*. See section 3.2.S.2.3 for further guidance.

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

Where there are multiple manufacturing sites for one API manufacturer, a comprehensive list in tabular form should be provided comparing the processes at each site and highlighting any differences.

All solvents used in the manufacture (including purification and/or crystallization step(s)) should be clearly identified. Solvents used in the final steps should be of high purity. Use of recovered solvents in the final steps of purification and/or crystallization is not recommended.

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

Justification should be provided for alternate manufacturing processes. Alternate processes should be explained with the same level of detail as the primary process. It should be demonstrated that batches obtained by the alternate processes have the same impurity profile as the principal process. If the obtained impurity profile is different it should be demonstrated to be acceptable according to the requirements described under S.3.2.

3.2.S.2.3 Control of materials

Materials used in the manufacture of the API (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed, identifying where each material is used in the process. Information on the quality and control of these materials should be provided. Information demonstrating that materials meet standards appropriate for their intended use should be provided.

In general, the starting material for synthesis described in the marketing authorization dossier should:

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

- be a well characterized, isolated and purified substance with its structure fully

elucidated including its stereochemistry (when applicable);

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

- be incorporated as a significant structural fragment into the structure of the API.

Copies of the specifications for the materials used in the synthesis, extraction, isolation and purification steps should be provided in the PD, including starting materials, reagents, solvents, catalysts and recovered materials. Confirmation should be provided that the specifications apply to materials used at each manufacturing site. A certificate of analysis of the starting material for synthesis should be provided. A summary of the information on starting materials should be provided in the QOS-PD.

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

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

3.2.S.2.4 Controls of critical steps and intermediates

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

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

The critical steps should be identified. These can be among others: steps where significant impurities are removed or introduced, steps introducing an essential molecular structural element such as a chiral centre or resulting in a major chemical transformation, steps having an impact on solid-state properties and homogeneity of the API that may be relevant for use in solid dosage forms.

Specifications for isolated intermediates should be provided and should include tests and acceptance criteria for identity, purity and assay, where applicable.

3.2.S.2.5 Process validation and/or evaluation

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

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

3.2.S.3 Characterization

3.2.S.3.1 Elucidation of structure and other characteristics

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

The MA application should include quality assurance (QA) certified copies of the spectra, peak assignments and a detailed interpretation of the data of the studies performed to elucidate and/or confirm the structure of the API. The QOS should include a list of the studies performed and a conclusion from the studies (e.g. if the results support the proposed structure).

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

For APIs that are described in an officially recognized pharmacopoeia, it is generally sufficient to provide copies of the IR spectrum of the API from each of the proposed manufacturer(s) run concomitantly with a pharmacopoeial reference standard.

Isomerism/ Stereochemistry

Where the potential for stereoisomerism exists, a discussion should be included of the possible isomers that can result from the manufacturing process and the steps where chirality was introduced. The identity of the isomeric composition of the API to that of the API in the comparator product should be established. Information on the physical and chemical properties of the isomeric mixture or single enantiomer should be provided, as appropriate. The API specification should include a test to ensure isomeric identity and purity.

The potential for inter-conversion of the isomers in the isomeric mixture, or racemization of the single enantiomer should be discussed.

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

Polymorphism

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

Amorphous solids consist of disordered arrangements of molecules and do not possess a distinguishable crystal lattice. Solvates are crystal forms containing either stoichiometric or non-stoichiometric amounts of a solvent. If the incorporated solvent is water the solvates are also commonly known as hydrates.

Polymorphic forms of the same chemical compound differ in internal solid-state structure and, therefore, may possess different chemical and physical properties, including packing, thermodynamic, spectroscopic, kinetic, interfacial and mechanical properties. These properties can have a direct impact on API processability, pharmaceutical product manufacturability and product quality/performance, including stability, dissolution and bioavailability. Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences.

Applicants and API manufacturers are expected to have adequate knowledge about the polymorphism of the APIs used and/or produced. Information on polymorphism can come from the scientific literature, patents, compendia or other references to determine if polymorphism is a concern, e.g. for APIs that are not *BCS highly soluble.* In the absence of published data for APIs that are not *BSC highly soluble*, polymorphic screening will be necessary to determine if the API can exist in more than one crystalline form. Polymorphic screening is generally accomplished via crystallization studies using different solvents and conditions.

There are a number of methods that can be used to characterize the polymorphic forms of an API. Demonstration of a non-equivalent structure by single crystal X-ray diffraction is currently regarded as the definitive evidence of polymorphism. X-Ray diffraction can also be used to provide unequivocal proof of polymorphism. Other methods, including microscopy, thermal analysis (e.g. DSC, thermal gravimetric analysis and hot-stage microscopy) and spectroscopy (e.g. IR, Raman, solid-state nuclear magnetic resonance (ssNMR) is helpful to further characterize polymorphic forms. Where polymorphism is a concern, the applicants/ manufacturers of APIs should demonstrate that a suitable method, capable of distinguishing different polymorphs, is available to them.

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

a) Specifications for the solvent-free API in 3.2.S.2.4, if that compound is a synthetic precursor;
b) Specifications for the solvated API including appropriate limits on the weight ratio API to solvent (with data to support the proposed limits);

c) A description of the method used to prepare the solvate in 3.2.S.2.2.

Particle size distribution

For APIs whose particle size distribution will have influence on FPP processability, stability, content uniformity, dissolution and bioavailability, specifications should include controls on the particle size distribution.

3.2.S.3.2 Impurities

Information on impurities should be provided.

Details on the principles for the control of impurities (e.g. reporting, identification and qualification) are outlined in the ICH Q3A and Q3C impurity guidelines. Discussion should be provided of the potential and actual impurities arising from the synthesis, manufacture or degradation of the API. This should cover starting materials, by-products, intermediates, chiral impurities and degradation products and should include the chemical names, structures and origins. The discussion of pharmacopoeial APIs should not be limited to the impurities specified in the API monograph.
Refer: ICH Q3A: Impurities in New Drug Substances and ICH Q3C Impurities: Guideline for Residual Solvents

3.2.S.4 Control of the API

3.2.S.4.1 Specification

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

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

a) The s*tandard* declared by the applicant could be an officially recognized compendial standard (BP, JP, Ph.Eur, Ph.Int. and USP) or a house (manufacturer's) standard.

b) The *specification reference number and version (e.g. revision number and/or date)* should be provided for version control purposes.

c) For the analytical procedures, the *type* should indicate the kind of analytical procedure used (e.g. visual, IR, UV, HPLC, laser diffraction), the *source* refers to the origin of the analytical procedure (BP, JP, Ph.Eur, Ph.Int, USP, in-house) and the *version (e.g. code number/version/date)* should be provided for version control purposes.

In cases where there is more than one API manufacturer, the FPP manufacturer's API specifications should be one single compiled set of specifications that is identical for each manufacturer. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement "for API from manufacturer A" (e.g. in the case of residual solvents).

Any non-routine testing should be clearly identified as such and justified along with the proposal on the frequency of non-routine testing.

3.2.S.4.2 Analytical procedures

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

3.2.S.4.3 Validation of analytical procedures

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

Copies of the validation reports for the analytical procedures used to generate testing results provided in the PD, as well as those proposed for routine testing of the API by the FPP manufacturer, should be provided.

Tables should be used to summarize the validation information of the analytical procedures *of the FPP manufacturer* for determination of residual solvents, assay and purity of the API, in section 2.3.S.4.3 of the QOS. The validation data for other methods used to generate assay and purity data in the PD can be summarized in 2.3.S.4.4 (c) or 2.3.S.7.3 (b) of the QOS.

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

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

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

Refer ICHQ2: Validation of Analytical Procedures: Text and Methodology for more guidance

3.2.S.4.4 Batch analyses

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

provided should include batch number, batch size, date and production site of relevant API batches.

Copies of the certificates of analysis, both from the API manufacturer(s) and the FPP manufacturer, should be provided for the profiled batches and any company responsible for generating the test results should be identified. This data is used to evaluate consistency in API quality. The FPP manufacturer's test results should be summarized in the QOS.

For quantitative tests (e.g. individual and total impurity tests and assay tests), it should be ensured that actual *numerical results* are provided rather than vague statements such as "within limits" or "conforms".

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).

3.2.S.4.5 Justification of specification

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

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

Refer ICH Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances, for more guidance

3.2.S.5 Reference standards or materials

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

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

A suitable primary reference standard should be obtained from an officially recognized pharmacopoeial source (BP, JP, Ph.Eur, Ph.Int, USP) where one exists and the lot number should be provided. Primary reference standards from officially recognized pharmacopoeial sources do not need further structural elucidation.

Otherwise a primary standard may be a batch of the API that has been fully characterized

(e.g. by IR, UV, NMR, MS analyses). Further purification techniques may be needed to render the material acceptable for use as a chemical reference standard. The purity requirements for a chemical reference substance depend upon its intended use. A chemical reference substance proposed for an identification test does not require meticulous purification, since the presence of a small percentage of impurities in the substance often has no noticeable effect on the test. On the other hand, chemical reference substances that are to be used in assays should possess a high degree of purity (such as 99.5% on the dried or water-/solvent-free basis). Absolute content of the primary reference standard must be declared and should follow the scheme:

100% minus organic impurities (quantitated by an assay procedure, e.g. HPLC, DSC, etc.) minus inorganic impurities minus volatile impurities by loss on drying (or water content minus residual solvents).

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

3.2.S.6 Container-closure system

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

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

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

Primary packaging components are those that are in direct contact with the API or FPP. The specifications for the primary packaging components should be provided and should include a specific test for identification (e.g. IR).

Copies of the labels applied on the secondary packaging of the API should be provided and should include the conditions of storage. In addition, the name and address of the manufacturer of the API should be stated on the container, regardless of whether re-labelling is conducted at any stage during the API distribution process.

3.2.S.7 Stability

Refer the Guidelines on Stability Requirements for Testing Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs).

b) Option 2: Certificate of suitability of European Pharmacopeia (CEP)

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

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

Along with the CEP the applicant should supply the following information in the dossier, with data summarized in the QOS-PD:-

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

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

c) *3.2.S.4.1 Specification* – the specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur monograph and any additional tests and acceptance criteria that are not controlled in the CEP and Ph.Eur monograph, such as polymorphs and/or particle size distribution.

d) *3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation* – for any tests in addition to those in the CEP and Ph.Eur monograph.

e) *3.2.S.4.4 Batch analysis* – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.

f) *3.2.S.5 Reference standards or materials* – information on the FPP manufacturer's reference standards.

g) *3.2.S.6 Container-closure system* – specifications including descriptions and identification of primary packaging components.

h) *3.2.S.7 Stability* – exception: where the CEP specifies a re-test period that is the same as or of longer duration than the re-test period proposed by the applicant.

i) In the case of sterile APIs, data on the sterilization process of the API, including validation data, should be included in the PD.

c) Option 3: Active pharmaceutical ingredient pre-qualified by WHO

A complete copy of the confirmation of API prequalification document should be provided in Module 1.

The applicant should supply the following information in the dossier, with data summarized in the QOS-PD:-

a) *3.2.S.1.3 General properties* – discussions on any additional applicable physicochemical and other relevant API properties that are not controlled by the API manufacturer's specifications, e.g. solubilities and polymorphs according to the guidance in this section.

b) *3.2.S.2* – if the sterility of the FPP is based upon the sterile manufacture of the API then data on the sterilization process together with full validation data should be provided.

c) *3.2.S.3.1 Elucidation of structure and other characteristics* – studies to identify polymorphs and particle size distribution, where applicable, according to the guidance in this section.

d) *3.2.S.4.1 Specification* – the specifications of the FPP manufacturer including all tests and limits of the API manufacturer's specifications and any additional tests and acceptance criteria that are not controlled by the API manufacturer's specifications such as polymorphs and/or particle size distribution.

e) *3.2.S.4.2/3.2.S.4.3 Analytical procedures and validation* – any methods used by the FPP manufacturer in addition to those in the API manufacturer's specifications.

f) 3.2.S.4.4 Batch analysis – results from two batches of at least pilot scale, demonstrating compliance with the FPP manufacturer's API specifications.

g) *3.2.S.5 Reference standards or materials* – information on the FPP manufacturer's reference standards.

h) *3.2.S.7 Stability* – data to support the retest period if either the proposed retest period is longer or the proposed storage conditions are at a higher temperature or humidity to that of the prequalified API.

Option 4: Active Pharmaceutical Ingredient Master File (APIMF)

Full details on the API information submitted by the API manufacturer, provided that the APIMF contains all information listed under Module 3.

It is the responsibility of the applicant to ensure that the API manufacturer's APIMF *restricted part* is supplied to the Authority directly by the API manufacturer when required. A copy of the letter of access should be provided in the product dossier in *Module 1*.

APIMF holders can use the guidance provided for the option "Full details in the" for preparation of the relevant sections of the Open and Restricted parts of their APIMFs.

3.2.P Finished pharmaceutical product (FPP)

3.2. P.1 Description and Composition of the FPP

A description of the FPP and its composition should be provided. The information provided should include:

1. Description of the dosage form

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

2. Composition

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

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

All ingredients used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 mg of active ingredient base = 1.075 mg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "contains 2% overage of the API to compensate for manufacturing losses").

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

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

- **Description of accompanying reconstitution diluent(s)**

For FPPs supplied with reconstitution diluent(s) that have been assessed and considered acceptable (registered) in connection with another product dossier, a brief description of the reconstitution diluents(s) should be provided.

For FPPs supplied with reconstitution diluent(s) have not been assessed and considered acceptable in connection with another product dossier, the information on the diluent(s) should be provided in a separate FPP portion ("3.2.P"), as appropriate.

- **Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable**

The container-closure used for the FPP (and accompanying reconstitution diluent, if applicable) should be briefly described, with further details provided under 3.2.P.7 Container-closure system, e.g. "The product is available in HDPE bottles with polypropylene caps (in sizes of 100s, 500s and 1000s) and in PVC/aluminium foil unit dose blisters (in packages of 100s) (cards of 5 × 2, 10 cards per package)."

3.2.P.2 Pharmaceutical development

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

Pharmaceutical development information should include, at a minimum:

a) the definition of the quality target product profile (QTPP) as it relates to quality, safety and efficacy, considering for example the route of administration, dosage form, bioavailability, strength and stability;

b) identification of the potential critical quality attributes (CQAs) of the FPP so as to adequately control the product characteristics that could have an impact on quality;

c) discussion of the potential CQAs of the API(s), excipients and container-closure system(s) including the selection of the type, grade and amount to deliver drug product of the desired quality; and

d) discussion of the selection criteria for the manufacturing process and the control strategy required to manufacture commercial lots meeting the QTPP in a consistent manner.

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

3.2.P.2.1 Components of the FPP

3.2.P.2.1.1 Active pharmaceutical ingredient

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

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

3.2.P.2.1.2 Excipients

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

3.2.P.2.2 Finished pharmaceutical product

3.2.P.2.2.1 Formulation development

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

If the proposed FPP is a functionally scored tablet, a study should be undertaken to ensure the uniformity of dose in the tablet fragments. The data provided in the PD should include a description of the test method, individual values, mean and relative standard deviation (RSD) of the results. Uniformity testing (i.e. content uniformity or mass variation, depending on the requirement for the whole tablet) should be performed on each split portion from a minimum of 10 randomly selected whole tablets.

In vitro dissolution or drug release

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

The results of studies justifying the choice of in vitro dissolution or drug release conditions (e.g. apparatus, rotation speed, medium) should be provided.

Data should also be submitted to demonstrate whether the method is sensitive to changes in manufacturing processes and/or changes in grades and/or amounts of critical excipients and particle size where relevant. The dissolution method should be sensitive to any changes in the product that would result in a change in one or more of the

pharmacokinetic parameters.

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

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

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

3.2.P.2.2.2 Overages

Any overages in the formulation(s) described in 3.2.P.1 should be justified. Justification of an overage to compensate for loss during manufacture should be provided, including the step(s) where the loss occurs, the reasons for the loss and batch analysis release data (assay results).

Overages for the sole purpose of extending the shelf-life of the FPP are generally not acceptable.

3.2. P.2.2.3 Physicochemical and biological properties

Parameters relevant to the performance of the FPP, such as pH, ionic strength, dissolution, re-dispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency and/or immunological activity, should be addressed.

3.2.P.2.3 Manufacturing process development

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

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

Differences between the manufacturing process(es) used to produce comparative bioavailability or bio-waiver batches and the process described in 3.2.P.3.3 that can

influence the performance of the product should be discussed.

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

3.2.P.2.4 Container-closure system

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

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

3.2.P.2.5 Microbiological attributes

Where appropriate the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products the integrity of the container-closure system to prevent microbial contamination should be addressed.

Where an antimicrobial preservative is included in the formulation, the amount used should be justified by submission of results of the product formulated with different concentrations of the preservative(s) to demonstrate the least necessary but still effective concentration. The effectiveness of the agent should be justified and verified by appropriate studies (e.g. USP or Ph.Eur general chapters on antimicrobial preservatives) using a batch of the FPP. If the lower limit for the proposed acceptance criterion for the assay of the preservative is less than 90.0%, the effectiveness of the agent should be established with a batch of the FPP containing a concentration of the antimicrobial preservative corresponding to the lower proposed acceptance criteria.

3.2.P.2.6 Compatibility

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.

Where a device is required for oral liquids or solids (e.g. solutions, emulsions, suspensions and powders/granules for such reconstitution) that are intended to be administered immediately after being added to the device, the compatibility studies mentioned in the following paragraphs are not required.

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

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

Refer ICH Q8 guidelines: Pharmaceutical Development for more guidance

Note: For an established non sterile generic product, a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) of the PD and QOS **(Annex VII)**

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s) (name, physical address)

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

The facilities involved in the manufacturing, packaging, labelling and testing should be listed. If certain companies are responsible only for specific steps (e.g. manufacturing of an intermediate) it should be clearly indicated. The list of manufacturers/companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block(s) and unit(s)), rather than the administrative offices.

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

Regulatory situation in other countries

The countries should be listed in which this product has been granted a marketing authorization (attach evidence for marketing authorization), this product has been withdrawn from the market and/or this application for marketing has been rejected, deferred or withdrawn. (Module 1, 1.10 Regulatory Status).

3.2.P.3.2 Batch formula

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

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

All ingredients used in the manufacturing process should be included, including those that may not be added to every batch (e.g. acid and alkali), those that may be removed during processing (e.g. solvents) and any others (e.g. nitrogen, silicon for stoppers). If the FPP is formulated using an active moiety, then the composition for the active ingredient should be clearly indicated (e.g. "1 kg of active ingredient base = 1.075 kg active ingredient hydrochloride"). All overages should be clearly indicated (e.g. "Contains 5 kg (corresponding to 2%) overage of the API to compensate for manufacturing losses").

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

3.2.P.3.3 Description of manufacturing process and process controls

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

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

Steps in the process should have the appropriate process parameters identified, such as time, temperature or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in section 3.2.P.3.4. In certain cases, environmental conditions (e.g. low humidity for an effervescent product) should be stated.

The maximum holding time for bulk FPP prior to final packaging should be stated. The holding time should be supported by the submission of stability data, if longer than 30 days. For an aseptic FPP, the holding time of the filtered product prior to filling should be supported by the submission of stability data, if longer than 24 hours.

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

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

3.2.P.3.4 Controls of critical steps and intermediates

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

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

Examples of applicable in-process controls include:

(a) Granulations: moisture (limits expressed as a range), blend uniformity (e.g. low-dose tablets), bulk and tapped densities and particle size distribution;

(b) Solid oral products: average weight, weight variation, hardness, thickness, friability, and disintegration checked periodically throughout compression, weight gain during coating;

(c) Semi-solids: viscosity, homogeneity, pH;

(d) Transdermal dosage forms: assay of API–adhesive mixture, weight per area of coated patch without backing;

(e) Metered dose inhalers: fill weight or volume, leak testing, valve delivery;

(f) Dry powder inhalers: assay of API–excipient blend, moisture, weight variation of individually contained doses such as capsules or blisters;

(g) Liquids: pH, specific gravity, clarity of solutions;

(h) Parenterals: appearance, clarity, fill volume or weight, pH, filter integrity tests, particulate matter, leak testing of ampoules, pre-filtration and/or pre-sterilization bio-burden testing.

3.2.P.3.5 Process validation and/or evaluation

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

A product quality review may be submitted in lieu of the information below.

The following information should be provided:

a) A copy of the *process validation protocol*, specific to this FPP, that identifies the critical equipment and process parameters that can affect the quality of the FPP and defines

testing parameters, sampling plans, analytical procedures and acceptance criteria;

b) A *commitment* that three consecutive, production-scale batches of this FPP will be subjected to *prospective validation* in accordance with the above protocol. The applicant should submit a written commitment that information from these studies will be available for verification.

c) Validation information relating to the adequacy and efficacy of any sterilization process (e.g. pharmaceutical product, packaging component should be submitted.

The process validation protocol should include inter alia the following:

a) A reference to the current master production document;

b) A discussion of the critical equipment;

c) The process parameters that can affect the quality of the FPP (critical process parameters (CPPs)) including challenge experiments and failure mode operation;

d) Details of the sampling: sampling points, stages of sampling, methods of sampling and the sampling plans (including schematics of blender/storage bins for uniformity testing of the final blend);

e) The testing parameters/acceptance criteria including in-process and release specifications and including comparative dissolution profiles of validation batches against the batch(es) used in the bioavailability or biowaiver studies;

f) The analytical procedures or a reference to appropriate section(s) of the dossier;

g) The methods for recording/evaluating results; and

h) The proposed timeframe for completion of the protocol.

The manufacture of sterile FPPs needs a well-controlled manufacturing area (e.g. a strictly controlled environment, highly reliable procedures and appropriate in-process controls). A detailed description of these conditions, procedures and controls should be provided.

The sterilization process should be described in detail and evidence should be provided to confirm that it will produce a sterile product with a high degree of reliability and that the physical and chemical properties as well as the safety of the FPP will not be affected. Details such as temperature range and peak dwell time for an FPP and the container-closure should be provided. Although standard autoclaving cycles of 121 °C for 15 minutes or more would not need a detailed rationale, such justifications should be provided for reduced temperature cycles or elevated temperature cycles with shortened exposure times. If ethylene oxide is used, studies and acceptance criteria should control the levels of residual ethylene oxide and related compounds.

Filters used should be validated with respect to pore size, compatibility with the product, absence of extractables and lack of adsorption of the API or any of the components.

For the validation of aseptic filling of parenteral products that cannot be terminally sterilized, simulation process trials should be conducted. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. Results on microbial contamination levels should be provided.

Note: For an established generic product a product quality review may satisfy the requirements of sections 3.2.P.3.5 of the PD and QOS **(Annex VII).**

3.2.P.4 Control of excipients

3.2.P.4.1 Specifications

The specifications for excipients should be provided.

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

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

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

For excipients of natural origin, microbial limit testing should be included in the specifications.

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

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

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

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

3.2.P.4.2 Analytical procedures

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

3.2.P.4.3 Validation of analytical procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided as in accordance to ICHQ6A.

Copies of analytical validation information are generally not submitted for the testing of excipients, with the exception of the validation of in-house methods where appropriate.

3.2.P.4.4 Justification of specifications

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

A discussion of the tests that are supplementary to those appearing in the officially recognized compendial monograph should be provided.

Refer to ICHQ2A, ICHQ2B and ICHQ6A for more guidance

3.2.P.4.5 Excipients of human or animal origin

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

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

For these excipients from animal origin, a letter of attestation should be provided confirming that the excipients used to manufacture the FPP are *without* risk of transmitting agents of animal spongiform encephalopathies.

Refer:

- *ICH Q5A Viral safety Evaluation of Biotechnology Products derived from Cell Lines of Human or Animal Origin.*
- *ICH Q5D Quality of Biotechnological Products: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products.*
- *Q6B Test Procedures and Acceptance Criteria for Biotechnological/Biological Products.*

3.2.P.4.6 Novel excipients

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

3.2.P.5 Control of FPP

3.2.P.5.1 Specification(s)

The specification(s) for the FPP should be provided. A copy of the FPP specification(s) from the company responsible for the batch release of the FPP should be provided. The specifications should be dated and signed by the authorized personnel (i.e. the person in charge of the quality control and quality assurance departments) should be provided in the PD. Two separate sets of specifications may be set out: after packaging of the FPP (release) and at the end of the shelf-life. Any differences between release and shelf-life tests and acceptance criteria should be clearly indicated and justified.

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

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

Refer ICHQ3B, ICHQ3C, ICHQ6A for more guidance.

3.2.P.5.2 Analytical procedures

The analytical procedures used for testing the FPP should be provided. Copies of the in-house analytical procedures used during pharmaceutical development (if used to generate testing results provided in the PD) as well as those proposed for routine testing should be provided. Unless modified, it is not necessary to provide copies of officially recognized compendial analytical procedures.

Refer to ICHQ6A

3.2.P.5.3 Validation of analytical procedures

Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP should be provided.
Copies of the validation reports for the in-house analytical procedures used during pharmaceutical development (if used to support testing results provided in the MA

application) as well as those proposed for routine testing should be provided.

As recognized by regulatory authorities and pharmacopoeias themselves, verification of compendial methods can be necessary. The compendial methods, as published, are typically validated based on an API or an FPP originating from a specific manufacturer. Different sources of the same API or FPP can contain impurities and/or degradation products or excipients that were not considered during the development of the monograph. Therefore, the monograph and compendial method(s) should be demonstrated suitable for the control of the proposed FPP.

For officially recognized compendial FPP *assay* methods, verification should include a demonstration of specificity, accuracy and repeatability (method precision). If an officially recognized compendial method is used to control related substances that are not specified in the monograph, full validation of the method is expected with respect to those related substances.

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

Refer to ICHQ2A and ICHQ2B for more guidance

3.2.P.5.4 Batch analyses

A description of batches and results of batch analyses should be provided.

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

Analytical results tested by the company responsible for the batch release of the FPP should be provided for not less than three batches of at least one commercial scale batch and two pilot scale batches. Copies of the certificates of analysis for these batches should be provided and the company responsible for generating the testing results should be identified.

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

A discussion and justification should be provided for any incomplete analyses (e.g. results not tested according to the proposed specification).
Refer ICH Q3B, Q3C and Q6A for more guidance.

3.2.P.5.5 Characterization of impurities

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

A discussion should be provided of all impurities that are potential degradation products (including those among the impurities identified in 3.2.S.3.2 as well as potential degradation products resulting from interaction of the API with other APIs (FDCs), excipients or the container-closure system) and FPP process-related impurities (e.g. residual solvents in the manufacturing process for the FPP).

Refer ICH Q3B, Q3C and Q6A for more guidance.

3.2.P.5.6 Justification of specification(s)

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

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

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

Refer to ICHQ6A

3.2.P.6 Reference standards or materials

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".

See Section 3.2.S.5 for information that should be provided on reference standards or materials. Information should be provided on reference materials of FPP degradation products, where not included in 3.2.S.5.

Refer to ICHQ6A

3.2.P.7 Container-closure system

A description of the container-closure systems should be provided, including the identity of materials of construction of each primary packaging component and its specification.

The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

For non-functional secondary packaging components (e.g. those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided. For functional secondary packaging components, additional information should be provided.

Suitability information should be located in 3.2.P.2.

Descriptions, materials of construction and specifications should be provided for the packaging components that are:

a) In direct contact with the dosage form (e.g. container, closure, liner, desiccant, filler);
b) Used for drug delivery (including the device(s) for multi-dose solutions, emulsions, suspensions and powders/granules for such);
c) Used as a protective barrier to help ensure stability or sterility; and
d) Necessary to ensure FPP quality during storage and shipping.

Specifications for the primary packaging components should include a specific test for identification (e.g. IR). Specifications for film and foil materials should include limits for thickness or area weight.

Refer FDA Guidance for Industry Container Closure Systems for Packaging Human Drugs and Biologics for more guidance.

3.2.P.8 Stability

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.

Refer the Guidelines on Stability Requirements for Testing Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs).

3.2. REGIONAL INFORMATION

3.2.R1 Production documentation

Submit Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application. English translations of executed records should be provided where relevant.

2.3.R.1.2 Master Production Documents

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

a) master formula;
b) dispensing, processing and packaging sections with relevant material and operational details;
c) relevant calculations (e.g. if the amount of API is adjusted based on the assay results or on the anhydrous basis);
d) identification of all equipment by, at a minimum, type and working capacity (including make, model and equipment number, where possible);
e) process parameters (e.g. mixing time, mixing speed, milling screen size, processing temperature range, granulation end-point and tablet machine speed (expressed as target and range));
f) list of in-process tests (e.g. appearance, pH, assay, blend uniformity, viscosity, particle size distribution, loss on drying, weight variation, hardness, disintegration time, weight gain during coating, leaker test, minimum fill, clarity and filter integrity checks) and specifications;
g) sampling plan with regard to the:
    - steps at which sampling should be done (e.g. drying, lubrication and compression),
    - number of samples that should be tested (e.g. for blend uniformity testing of low-dose FPPs, blend drawn using a sampling thief from x positions in the blender),
    - frequency of testing (e.g. weight variation every x minutes during compression or capsule filling);
h) precautions necessary to ensure product quality (e.g. temperature and humidity control and maximum holding times);
i) for sterile products, reference to standard operating procedures (SOPs) in appropriate sections and a list of all relevant SOPs at the end of the document;
j) theoretical and actual yield;
k) compliance with the GMP requirements.

2.3.R.2 Analytical Procedures and Validation Information

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

MODULE 4: NON CLINICAL STUDY REPORTS

This chapter presents an agreed format for the organization of the nonclinical reports in the Common Technical Document for applications that will be submitted to the Authority.

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

4.1 Table of Contents of Module 4

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

4.2 Study Reports

The study reports should be presented in the following order:

4.2.1 Pharmacology

Refer ICH Guideline on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and marketing authorization for Pharmaceuticals (M3) for the nonclinical safety studies recommended to support human clinical trials of a given scope and duration as well as marketing authorization for pharmaceuticals.

Refer ICH Guideline on Safety Pharmacology Studies for Human Pharmaceuticals (S7A) for the definition, objectives and scope of safety pharmacology studies. It also addresses which studies are needed before initiation of Phase 1 clinical studies as well as information needed for marketing.

Refer ICH Guideline on The Non-Clinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals (S7B) for a non-clinical testing strategy for assessing the potential of a test substance to delay ventricular repolarization. This Guideline includes information concerning non-clinical assays and integrated risk assessments.

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

Refer ICH Guideline on Pharmacokinetics: Guidance for Repeated Dose Tissue Distribution Studies (S3B) for guidance on circumstances when repeated dose tissue distribution studies should be considered (i.e., when appropriate data cannot be derived from other sources). It also gives recommendations on the conduct of such studies.

4.2.3 Toxicology

Refer ICH Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (S3A) for guidance on developing test strategies in toxicokinetics and the need to integrate pharmacokinetics into toxicity testing, in order to aid in the interpretation of the toxicology findings and promote rational study design development.

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)

Refer The Committee for Human Medicinal Products (CHMP) Guideline on repeated dose toxicity for guidance on the conduct of repeated dose toxicity studies of active substances intended for human use.

Refer ICH Guideline on Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing) (S4) for the considerations that apply to chronic toxicity testing in rodents and non-rodents as part of the safety evaluation of a medicinal product. The text incorporates the guidance for repeat-dose toxicity tests.

4.2.3.3 Genotoxicity

Refer ICH Guidance on Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use (S2) for specific guidance and recommendations for in vitro and in vivo tests and on the evaluation of test results. This document addressed two fundamental areas of genotoxicity testing: the identification of a standard set of assays to be conducted for registration, and the extent of confirmatory experimentation in any particular genotoxicity assay in the standard battery.

Refer the committee for medicinal products for human use (CHMP) guideline on the limits of genotoxic impurities for a general framework and practical approaches on how to deal with genotoxic impurities in new active substances. It also relates to new applications for existing active substances, where assessment of the route of synthesis, process control and impurity profile does not provide reasonable assurance that no new or higher levels of genotoxic impurities are introduced as compared to products currently authorized in the EU containing the same active substance. The same also applies to variations to existing Marketing Authorizations pertaining to the synthesis.

4.2.3.3.1 In vitro
4.2.3.3.2 In vivo (including supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

Refer ICH Guideline on Need for Carcinogenicity Studies of Pharmaceuticals (S1A) for a consistent definition of the circumstances under which it is necessary to undertake carcinogenicity studies on new drugs. These recommendations take into account the known risk factors as well as the intended indications and duration of exposure.

Refer ICH Guideline on Testing for Carcinogenicity of Pharmaceuticals (S1B) for guidance on the need to carry out carcinogenicity studies in both mice and rats, and guidance is also given on alternative testing procedures, which may be applied without jeopardizing safety.

Refer ICH Guideline on Dose Selection for Carcinogenicity Studies of Pharmaceuticals (S1C) for the criteria for selection of the high dose for carcinogenicity studies of therapeutics. The use of other pharmacodynamic-, pharmacokinetic-, or toxicity-based endpoints in study design should be considered based on scientific rationale and individual merits.

4.2.3.4.1 Long-term studies (in order by species; including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)
4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity (including range-finding studies and supportive toxicokinetics evaluations) (If modified study designs are used, the following sub-headings should be modified accordingly.)

Refer ICH Guidance on Detection of Toxicity to Reproduction for Medicinal Products & Toxicity to Male Fertility (S5) for guidance on tests for reproductive toxicity. It defines the periods of treatment to be used in animals to better reflect human exposure to medical products and allow more specific identification of stages at risk.

Refer committee for medicinal products for human use (CHMP) guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications for guidance on the need for, role and timing of studies in juvenile animals in the non-clinical safety evaluation of medicinal products for paediatric use.

4.2.3.5.1 Fertility and early embryonic development
4.2.3.5.2 Embryo-foetal 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

Refer the Committee for medicinal products for human use (CHMP) guideline on Non-clinical local tolerance testing of medicinal products for recommendations on the evaluation of local tolerance to be performed prior to human exposure to the product. The purpose of these

studies is to ascertain whether medicinal products are tolerated at sites in the body, which may come into contact with products as the result of its administration in clinical use.

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity
4.2.3.7.2 Immunotoxicity

Refer ICH Guideline on Immunotoxicity Studies for Human Pharmaceuticals (S8) for the recommendations on nonclinical testing for immunosuppression induced by low molecular weight drugs (non-biologicals). It applies to new pharmaceuticals intended for use in humans, as well as to marketed drug products proposed for different indications or other variations on the current product label in which the change could result in unaddressed and relevant toxicologic issues. In addition, the Guideline might also apply to drugs in which clinical signs of immunosuppression are observed during clinical trials and following approval to market.

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 toxicity studies
4.2.3.7.7.1 Photosafety evaluation

A harmonized guideline on photosafety evaluation of pharmaceuticals is to be published through the ICH process.

For generic products are generally exempted in this module; however, in some cases such as changes in safety impurity profile, the safety assessment studies should be conducted.

For specific products

Refer ICH Guideline on clinical Evaluation for Anticancer Pharmaceuticals (S9) for information for pharmaceuticals that are only intended to treat cancer in patients with late stage or advanced disease regardless of the route of administration, including both small molecule and biotechnology-derived pharmaceuticals. It describes the type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals and references other guidance as appropriate.

Refer ICH Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (S6) for the pre-clinical safety testing requirements for biotechnological products. It addresses the use of animal models of disease, determination of when genotoxicity assays and carcinogenicity studies should be performed, and the impact of antibody formation on duration of toxicology studies.

Refer committee for medicinal products for human use (CHMP) guideline on Non-clinical development of fixed combinations of medicinal products for guidance on the non-clinical strategies to be considered when developing a fixed combination based on the different data available in order to support the safe human use as well as avoid unnecessary repetition of animal studies.

MODULE 5: CLINICAL STUDY REPORTS

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

Preamble

Through the ICH process, a guideline has been published on the structure and content of clinical study reports (E3). This document provides guidance on the organization of these study reports, other clinical data, and references within a Common Technical Document (CTD) for registration of a pharmaceutical product for human use. These elements should facilitate the preparation and review of a marketing application.
This guideline is not intended to indicate what studies are required for successful registration. It indicates an appropriate organization for the clinical study reports that are in the application.

Detailed Organization of Clinical Study Reports and Related Information in Module 5

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

5.1 Table of Contents of Module 5

A Table of Contents for study reports should be provided.

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability (BA) Study Reports
5.3.1.2 Comparative BA and Bioequivalence (BE) Study Reports

For Generic product

Refer Guidelines on Therapeutic Equivalence Requirements.

5.3.1.3 *In vitro-In vivo* Correlation Study Reports

For Generic product
Refer Guidelines on Therapeutic Equivalence Requirements.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

For Generic product

Refer Guidelines on Therapeutic Equivalence Requirements.

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 (PK) 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 (PD) 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
5.3.5.3 Reports of Analyses of Data from More Than One Study
5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-Marketing Experience if available

5.3.7 Case Report Forms and Individual Patient Listings

Refer Guidelines on Therapeutic Equivalence Requirements.

5.4 Literature References

Refer list of the ICH guidelines on clinical studies

For Section 5.2 and 5.4 refer ICH guidelines for detailed information on the requirements.

ANNEX I – 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 a registration of human medicines that details are as follows:

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

You will find enclosed the submission dossier as specified hereafter:

☐ CTD format, 2 soft copies documents format

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

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

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

☐ The electronic submission contains the following modules:
- Module 1: Administrative information and product information
- Module 2: Overview and summaries
- Module 3: Quality
- Module 4: Non clinical study reports
- Module 5: Clinical study reports

<The relevant fees have been paid.>

Yours sincerely,

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

ANNEX II: APPLICATION FORM

Application Number	Official use only
Date of submission of the dossier	Official use only
MODULE 1: ADMINISTRATIVE INFORMATION	
1.0 PARTICULARS OF THE PRODUCT	
1.1	Type of the medicinal product application New Generic Renewal* * If variation has been made, information supporting the changes should be submitted. See variation guidelines for registered medicinal products.
1.2	Proprietary Name
1.3	International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API)
1.4	Strength of Active Pharmaceutical Ingredient (API) per unit dosage form:
1.5	Name and address (physical and postal) of Applicant
(Company) Name: Address: Country: Telephone: Telefax: E-Mail:	
1.6	Pharmaceutical Dosage form* and route of administration* * List of standard terms for dosage forms and routes of administration is available on Guidelines on List of Standard Terms for Pharmaceutical Dosage Forms and Routes of Administration.
1.6.1	Dosage form:
1.6.2	Route(s) of administration (use current list of standard terms)
1.7	Packing/pack size:
1.8	Visual description (Add as many rows as necessary)
1.9	Proposed shelf life (in months):
1.9.1	Proposed shelf life (after reconstitution or dilution):
1.9.2	Proposed shelf life (after first opening container):
1.9.3	Proposed storage conditions:
1.9.4	Proposed storage conditions after first opening:
1.10	Other sister medicinal products registered or applied for registration
1.10.1	Do you hold Marketing Authorization (s) of other medicinal product (s) containing the same active pharmaceutical ingredient(s) in the EAC? If yes state; ▪ Product name (s), strength (s), pharmaceutical form (s): ▪ Partner States where product is authorized: ▪ Marketing authorization number(s): ▪ Indication(s):
1.10.2	Have you applied for Marketing Authorization medicinal product(s) containing the same active substance (s) in the EAC? ▪ Product name (s), strength (s), pharmaceutical form (s):

	▪ Indication(s):
1.11	Pharmacotherapeutic group and ATC Code
1.11.1	Pharmacotherapeutic group:
1.11.2	ATC Code: (Please use current ATC code)
1.11.3	If no ATC code has been assigned, please indicate if an application for ATC code has been made: ☐
1.12	Distribution category: Controlled Drug ☐ POM ☐ Pharmacy Only ☐ OTC ☐ General sale ☐ (Applicants are invited to indicate which categories they are requesting, however, the Authority reserve the right to change and/or apply only those categories provided for in their national legislation)
1.13	Country of origin:
1.14	Product Marketing Authorization in the country of origin (Attach Certificate of Pharmaceutical Product from National Medicines Regulatory Authority). If not registered, state reasons

☐Authorized Country: Date of authorization (dd-mm-yyyy): Proprietary name: Authorization number: ☐ Refused Country: Date of refusal (dd-mm-yyyy): Reason for Refusal:	☐ Withdrawn (by applicant after authorization) Country: Date of withdrawal (dd-mm-yyyy): Proprietary name: Reason for withdrawal: ☐ Suspended/revoked (by competent authority) Country: date of suspension/revocation (dd-mm-yyyy): Reason for suspension/revocation: Proprietary name:

1.15	List ICH countries and Observers where the product is approved.
1.16	Name(s) and complete physical address(es) of the manufacturer(s)
1.16.1	Name(s) and physical address (es) of the manufacturing site of the finished pharmaceutical product (FPP), including the final product release if different from the manufacturer. Alternative sites should be also declared here. All manufacturing sites involved in the manufacturing process of each step of the finished product, stating the role of each including quality control / in-process testing sites should be listed. (Add as many rows as necessary

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

1.16.2	Name(s) and physical address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s) (API)

	(Add as many rows as necessary) All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control / in-process testing sites should be listed.

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

1.17	Name and address (physical and postal) of the Brokers and Suppliers (if applicable)

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

1.18	Name and address (physical and postal) of the person or company responsible for Pharmacovigilance

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

1.19	State the reference/monograph standard such as British Pharmacopeia, United States Pharmacopeia, Ph. Eur, Japanese Pharmacopeia, In-house monograph e.t.c. used for Finished Pharmaceutical Product.
1.20	Qualitative and Quantitative composition of the active substance(s) and excipient(s) A note should be given as to which quantity the composition refers (e.g. 1 capsule).

Name of active ingredient(s)*	Quantity / dosage unit	Unit of measure	Reference/ monograph standard	
1.				
2.				
e.t.c				
Name of excipient(s)				
1.				
2.				
e.t.c				

Note: * Only one name for each substance should be given in the following order of priority: INN**, Pharmacopoeia, common name, scientific name
** The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.
Details of averages should not be included in the formulation columns but should be stated below:
- Active substance(s):
- Excipient(s):

1.21	Name and address (physical and postal) of the Contract Research Organisation(s) where the clinical studies of the product were conducted or name and address of laboratory where comparative dissolution studies in support of bio-waiver were conducted. (If applicable)

Name:
Company name:
Address:
Country:
Telephone:
Telefax:
E-Mail:

2.0 DECLARATION BY AN APPLICANT

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

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

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

I further agree that I am obliged to follow the requirements of the Legislations and Regulations, which are applicable to medicinal products.

I also consent to the processing of information provided by the Authority.

It is hereby confirmed that fees will be paid/have been paid according to the National/Community rules*

Name: ……
Position in the company:……
Signature: ……
Date:……
Official stamp:……

* Note: If fees have been paid, attach proof of payment

ANNEX III: EXPERT DECLARATION FORM

The following is an example of a suitable declaration form:

Quality /Non-clinical / Clinical (delete those not appropriate)

I, the undersigned, declare that I have:

i. The suitable technical or professional qualifications to act in this capacity (for more information, refer to the enclosed *curriculum* vitae).

ii. Fully examined the data provided by the applicant and have provided references to the literature to support statements made that are not supported by the applicant's original data. This report presents an objective assessment of the nature and extent of the data.

iii. Provided a report based on my independent assessment of the data provided.

iv. Based my recommendations, regarding suitability for registration, on the data provided herewith. I have considered the attached data and have recommended as to suitability for registration of the intended dose forms and presentations according to the proposed product information document.

I further declare that this expert report represents my own view.

Further, I declare the following to be the full extent of the professional relationship between the applicant and myself:

……

……

……

……

……

ANNEX IV: LETTER OF ACCESS TO CEP

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

<Applicant's reference> <Date>

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

Dear Sir/Madam,

Subject: Authorization to access Certificate of Suitability (CEP)

Reference is made to the above subject matter.

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

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

(Name of company or individual)

The API is manufactured by:
(*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 Authority before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except as permitted by the TFDA 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 country before written approval is granted by the Authority.

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

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

(*Name and address*)
Yours faithfully

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

ANNEX V: LETTER OF ACCESS TO APIMF

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

<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 of the Authority*) to make reference to this company's Active Pharmaceutical Ingredient Master File(s) for [API(s) name] in the evaluation of applications relating to the registration of [medicine name(s)] submitted to (*name of the Authority*) by the (*applicant's name*).

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

(Name of company or individual)

The substance is manufactured by:
(Names and addresses of all manufacturing sites and manufacturing steps carried out at site)

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

A formal agreement exists between the applicant of the medicine and the manufacturer of the API, which ensures that information, will be communicated between them and to the Authority before any significant change is made to the site of manufacture, manufacturing procedure or quality control specifications of the API. Except as permitted by the 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 the country before written approval is granted by the Authority.

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

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

Any questions arising from the evaluation process of this APIMF should be forwarded to:

{Name and address}

Yours faithfully

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

ANNEX VI: QUALITY OVERALL SUMMARY – PRODUCT DOSSIER (QOS- PD)

Summary of product information:

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

2.3.S ACTIVE PHARMACEUTICAL INGREDIENT (API))

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

Name of API:	
Name of API manufacturer:	
□	Full details in the PD: Summaries of the full information should be provided under the appropriate sections; see Section 3.2.S in the Quality guideline.
□	Certificate of suitability to the European Pharmacopoeia (CEP): is a written commitment provided that the applicant will inform the Authority in the event that the CEP is withdrawn and has acknowledged that withdrawal of the CEP will require additional consideration of the API data requirements to support the dossier: □ yes, □ no; a copy of the most current CEP (with annexes) and written commitment should be provided in *Module 1*; the declaration of access should be filled out by the CEP holder on behalf of the FPP manufacturer or applicant who refers to the CEP; and summaries of the relevant information should be provided under the appropriate sections (e.g. S.1.3, S.3.1, S.4.1 through S.4.4, S.6 and S.7; see Quality guideline).
□	Active pharmaceutical ingredient pre-qualified by WHO Provide evidence

□	EAC Active pharmaceutical ingredient master file (APIMF): A copy of the letter of access should be provided in *Module 1*; and summaries of the relevant information from the Open part should be provided under the appropriate sections; see Section 3.2.S in the Quality guideline.

2.3.S.1 General Information

2.3.S.1.1 Nomenclature

(a) (Recommended) International Non-proprietary name (INN):
(b) Compendial name, if relevant:
(c) Chemical name(s):
(d) Company or laboratory code:
(e) Other non-proprietary name(s) (e.g. national name, USAN, BAN):
(f) Chemical Abstracts Service (CAS) registry number:

2.3.S.1.2 Structure

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

2.3.S.1.3 General Properties

(a) Physical description (e.g. appearance, colour, physical state):
(b) Solubilities:
In common solvents:
Quantitative aqueous pH solubility profile (pH 1 to 6.8):

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

2.3.S.2.1 Manufacturer(s)

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

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

(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

(a) 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**

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

2.3.S.2.4 Controls of Critical Steps and Intermediates

(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

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

2.3.S.2.6 Manufacturing Process Development

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

2.3.S.3 Characterisation

2.3.S.3.1 Elucidation of Structure and other Characteristics

(a) List of studies performed (e.g. IR, UV, NMR, MS, elemental analysis) and conclusion from the studies (e.g. whether results support the proposed structure):
(b) Discussion on the potential for isomerism and identification of stereochemistry (e.g. geometric isomerism, number of chiral centres and configurations) of the API batch(es) used in comparative bioavailability or biowaiver studies:
(c) Summary of studies performed to identify potential polymorphic forms (including solvates):
(d) Summary of studies performed to identify the particle size distribution of the API:
(e) Other characteristics:

2.3.S.3.2 Impurities

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

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

API-related impurity (chemical name or descriptor)	Structure	Origin

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

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

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

(i) Maximum daily dose (i.e. the amount of 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**)		

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

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

(iii) Justification of proposed acceptance criteria for impurities:

2.3.S.4 Control of the API

2.3.S.4.1 Specification

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

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

2.3.S.4.2 Analytical Procedures

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

2.3.S.4.3 Validation of Analytical Procedures

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

2.3.S.4.4 Batch Analyses

(a) Description of the batches:

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

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

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

(c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.S.4.2 and 2.3.S.4.3 (e.g. historical analytical procedures):

2.3.S.4.5 Justification for Specification

(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

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

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

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

2.3.S.6 Container Closure System

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

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

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

2.3.S.7 Stability

2.3.S.7.1 Stability Summary and Conclusions

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

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

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

Storage condition (◦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	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

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

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

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

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

2.3.S.7.3 Stability Data

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

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

2.3.P FINISHED PHARMACEUTICAL PRODUCT (FPP)

2.3.P.1 Description and Composition of the FPP

(a) Description of the FPP:

(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	**%**	**Quant. per unit**	**%**	**Quantity per unit**	**%**
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>							
Subtotal 1							
<complete with appropriate title e.g. Film-coating >							
Subtotal 2							
Total							

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

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

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

2.3.P.2 Pharmaceutical Development

2.3.P.2.1 Components of the FPP

2.3.P.2.1.1 Active Pharmaceutical Ingredient

(a) Discussion of the:

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

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

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

2.3.P.2.1.2 Excipients

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

2.3.P.2.2 Finished Pharmaceutical Product

2.3.P.2.2.1 Formulation Development

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

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

(i) Summary of batch numbers:

Batch number(s) of the FPPs used in			
Bioequivalence or biowaiver			
Dissolution profile studies			
Stability studies (primary batches)			
‹packaging configuration I›			
‹ packaging configuration II›			
‹*Add/delete as many rows as necessary*›			
Stability studies (production batches)			
‹ packaging configuration I›			
‹ packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (primary batches) if available			

‹ packaging configuration I›			
‹ packaging configuration II›			
(Add/delete as many rows as necessary)			
Validation studies (at least the first three consecutive production batches) or code(s)/version(s) for process validation protocol(s)			

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

Component and quality standard (e.g. NF, BP, Ph.Eur, in-house)	**Relevant batches**							
	Comparative bioavailability or 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>**	
	Theoretical quantity per batch	**%**	**Theoretical quantity per batch**	**%**	**Theoretical quantity per batch**	**%**	**Theoretical quantity per batch**	**%**
<complete with appropriate title e.g. Core tablet, Contents of capsule, Powder for injection>								
Subtotal 1								
<complete with appropriate title e.g. Film-coating >								
Subtotal 2								
Total								

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

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

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

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

2.3.P.2.2.2 Overages

(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):

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**

2.3.P.3.2 Batch Formula

(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/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 title e.g. Core tablet, Contents of capsule, Powder for injection>			
Subtotal 1			
<complete with appropriate title e.g. Film-coating >			
Subtotal 2			
Total			

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

(a) Flow diagram of the manufacturing process:

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

(c) Justification of reprocessing of materials:

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**

2.3.P.3.5 Process Validation and/or Evaluation

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

2.3.P.4 Control of Excipients

2.3.P.4.1 Specifications

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

2.3.P.4.2 Analytical Procedures

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

2.3.P.4.3 Validation of Analytical Procedures

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

2.3.P.4.4 Justification of Specifications

(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: (page and volume)

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

2.3.P.4.6 Novel Excipients

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

2.3.P.5 Control of FPP

2.3.P.5.1 Specification(s)

Specification(s) for the FPP:

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

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

2.3.P.5.2 Analytical Procedures

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

2.3.P.5.3 Validation of Analytical Procedures

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

2.3.P.5.4 Batch Analyses

(a) Description of the batches:

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

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

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

(c) Summary of analytical procedures and validation information for those procedures not previously summarized in 2.3.P.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 (chemical name or descriptor)	**Structure**	**Origin**

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

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

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

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

(ii) Data on observed impurities for relevant batches (e.g. comparative bioavailability or 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**	**Container size**

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

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

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

2.3.P.8 Stability

2.3.P.8.1 Stability Summary and Conclusions

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

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

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

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

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

(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)		
Tests and acceptance criteria	Description	
	Moisture	
	Impurities	
	Assay	
	etc.	

Parameter	Details
Testing frequency	
Container closure system(s)	

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

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

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

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

2.3.P.8.3 Stability Data

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

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

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

2.3.R REGIONAL INFORMATION

2.3.R.1 Production Documentation

2.3.R.1.1 Executed Production Documents

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

2.3.R.1.2 Master Production Documents

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

2.3.R.2 Analytical Procedures and Validation Information

ANALYTICAL PROCEDURES AND VALIDATION INFORMATION SUMMARIES

ATTACHMENT NUMBER:	

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

ATTACHMENT NUMBER:	

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

ANNEX VII: PRODUCT QUALITY REVIEW (PQR) REQUIREMENTS FOR GENERIC PHARMACEUTICAL PRODUCTS

For an established generic product a product quality review may satisfy the requirements of sections 3.2.P.2.2.1 (a), 3.2.P.2.3 (a) and 3.2.P.3.5 of the PD and QOS-PD.

A product quality review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.

Reviews should be conducted with not less than 10 consecutive batches manufactured over the period of the last 12 months, or, where 10 batches were not manufactured in the last 12 months, not less than 25 consecutive batches manufactured over the period of the last 36 months and should include at least:

1. A review of starting and primary packaging materials used in the FPP, especially those from new sources.
2. A tabulated review and statistical analysis of quality control and in-process control results.
3. A review of all batches that failed to meet established specification(s).
4. A review of all critical deviations or non-conformances and related investigations.
5. A review of all changes carried out to the processes or analytical methods.
6. A review of the results of the stability-monitoring programme.
7. A review of all quality-related returns, complaints and recalls, including export- only medicinal products.
8. A review of the adequacy of previous corrective actions.
9. A list of validated analytical and manufacturing procedures and their revalidation dates.

Notes

Reviews must include data from all batches manufactured during the review period. Data should be presented in tabular or graphical form (i.e. charts or graphs), when applicable.