EAST AFRICAN COMMUNITY

COMPENDIUM OF MEDICINES EVALUATION AND REGISTRATION FOR MEDICINE REGULATION HARMONIZATION IN THE EAST AFRICAN COMMUNITY

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FOREWARD

This Compendium has been developed to provide guidance to National Medicines Regulatory Authorities in managing applications for registration of human medicinal products in the East African Community.

It was compiled by the Technical Working Group (TWG) on Medicines Evaluation and Registration (MER) of the East African Community Medicine Regulatory Harmonization (EAC MRH) Project. The group relied on their experiences and knowledge on medicines registration requirements of their individual Countries, World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Registration of Medicines for Human Use (ICH) and other available literature.

EAC Secretariat is highly indebted to African Medicines Regulatory Harmonization (AMRH) programme partners, namely the World Health Organization for their technical support; Bill and Melinda Gates Foundation (BMGF) for financial support, the World Bank for establishing AMRH trust fund and financial management; the United Kingdom Department for International Development (DFID) for their financial assistance and African Union New Partnership for Africa's Development (AU-NEPAD) for high level advocacy. I also wish to recognize the contribution of Clinton Health Access Initiative (CHAI) in the conceptualization stage of African Medicines Regulatory Harmonization initiative.

Regional coordination and commitment for implementation of the East African Medicines Regulation Harmonization (MRH) Programme by EAC Secretariat Staff is acknowledged.

In addition, progressive monitoring of the project by the regional steering committee to ensure set milestones are achieved is highly appreciated.

Finally, I would like to acknowledge regional stakeholders including the respective Ministries responsible for the EAC Affairs and Health, the regional and international pharmaceutical industry and associations and the academia for their valuable inputs into this Compendium.

Ambassador Liberat Mfumukeko
EAC Secretary General

PREFACE

The “EAC Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products’ First Edition, April 2014’ is an EAC publication which sets out procedures and requirements for the implementation of Pharmaceutical Products Registration through established CTD within the EAC NMRAs. This Compendium contains Five Modules:

Module 1: the East African Community Medicinal Products Registration 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 harmonized medicines registration procedures using CTD in order to improve access to essential medicines for prevention and treatment of priority disease conditions in the East African region.

The East African Community Medicines Regulatory Harmonization (EAC-MRH) programme was established to help Partner States build effective medicines regulation procedures through harmonization and regulatory capacity building. Most of the EAC Partner States have challenges in assuring the safety, efficacy and quality of medicines circulating in their markets due to a number of factors including limited human and infrastructural capacity to regulate, varying standards of regulations, long procedures to introduce new medicines in the market.

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 who actively participated in the development and review of the guidelines. I therefore urge all technical experts from the Partner States National Medicines Regulatory Authorities and EAC Secretariat to use this

compendium as a tool to effectively carry out medicines evaluation and registration processes.

Hon. Christophe Bazivamo
Deputy Secretary General
Productive and Social Sectors

RESPONSIBILITY FOR IMPLEMENTATION OF THE COMPENDIUM OF COMMON TECHNICAL DOCUMENT (CTD) FOR HARMONIZATION OF MEDICINES EVALUATION AND REGISTRATION IN THE EAST AFRICAN COMMUNITY

The EAC Sectoral Council of Ministers of Health recognizes the work done by the EAC Secretariat in collaboration with the lead EAC Partner States National Medicines Regulatory Authorities (NMRAs), Tanzania Food and Drugs Authority (TFDA) for coordinating the development of harmonized medicines evaluation and registration guidelines and procedures. The harmonized technical common documents will facilitate uniformity in medicines evaluation and avoid duplication of efforts between Medicines Regulatory Authorities in the region.

Harmonization of medicines registration is an explicit policy priority under Chapter 21 (Article 118) of the EAC Treaty and vital in enabling the free movement of goods in line with the EAC Common Market Protocol. Streamlining medicines evaluation and registration procedures will have a positive impact to public health by increasing access to good quality, safe and efficacious medicines in the region.

The EAC Sectoral Council of Ministers of Health approves the use of these guidelines in the East African Community Partner States' National Medicines Regulatory Authorities (NMRAs) in accordance with the existing regional legal framework. Implementation of these documents will facilitate mutual recognition of regulatory decisions and attestation of the quality and safety of medicines, cosmetics, medical devices and diagnostics manufactured, produced, imported, exported or traded in East African Community.

The EAC Partner States Ministries responsible for Health shall be responsible for the enforcement of this Compendium of harmonised technical documents for Medicines Evaluation and Registration in the East African Community through the respective National Medicines Regulatory Authorities (NMRAs).

SIGNED by the Leaders of Delegation on this 26th October 2018;

Hon. Dr. Daniel Ngamije	**Hon. Mutahi Kagwe,EGH**	**Hon.Dr.Thaddée Ndikumana**	**Hon. Ummy Ally Mwalimu**	**Hon.Elizabeth Achuei Yol Kuol**	**Hon.Sarah Aceng Opendi**
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		HIV/AIDS			
Ministry of Health	Ministry of Health	Ministry of Public Health and Fight against HIV/AIDS	Ministry of Health, Community Development, Gender, Elderly and Children	Ministry of Health	Ministry of Health
REPUBLIC OF RWANDA	**REPUBLIC OF KENYA**	**REPUBLIC OF BURUNDI**	**THE UNITED REPUBLIC OF TANZANIA**	**REPUBLIC OF SOUTH SUDAN**	**REPUBLIC OF UGANDA**

PART I:

EAC GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF HUMAN PHARMACEUTICAL PRODUCTS

Abbreviations and acronyms

API	Active Pharmaceutical Ingredient
APIMF	Active Pharmaceutical Ingredient Master File
CEP	Certificate of Suitability to the monograph of Ph Eur monograph
CTD	Common Technical Document
EAC	East Africa Community
EAC-MRH	East Africa Medicines Registration Harmonization
EAC-NMRA	East Africa Partner State National Medicines Regulatory Authority
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

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.

Active pharmaceutical ingredient (API)

An active ingredient is 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.
(USFDA Glossary of terms, it can be found online at Drugs@FDA Glossary of Terms).

Active Pharmaceutical Ingredient (API) starting material

A raw material, intermediate, or an API that is used in the production of an API and that is incorporated as a significant structural fragment into the structure of the API. (*WHO Glossary of Terms*).

Market Authorization Holder (MAH)

Is a person resident/domiciled to each of the EAC Partner States who holds authorization to place a medicinal product in the EAC Partner Sates and is responsible for that product.

Commitment batches

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

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

Is 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.

(PHIS Glossary 2009, can be found online at: http://phis.goeg.at/index.aspx?alias=phisglossary)

Existing API

An API that is not considered a new active substance, which has been previously approved through a finished product by a stringent regulatory authority. (*WHO Glossary of Terms*).

Finished pharmaceutical product (FPP)

A finished dosage form of a pharmaceutical product which has undergone all stages of manufacture, including packaging in its final container and labelling. (*WHO Glossary of Terms*).

Innovator medicinal product

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

Manufacturer

A manufacturer is 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.

(PHIS Glossary 2009, can be found on line at: http://phis.goeg.at/index.aspx?alias=phisglossary)

Mock-up

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 in the EAC-MRH project 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

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. (*WHO Glossary of Terms*).

Pilot-scale batch

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

Primary batch

A batch of an API or FPP used in a stability study, from which stability data are submitted in a registration application for the purpose of establishing a retest period or shelf-life. (*WHO Glossary of Terms*).

Production batch

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

Specimen

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

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 submission to the EAC-NMRA. 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 EAC Guidelines on Procedural Aspects for Application for Market Authorization for Human Medicinal Products.

1.2 Scope

These guidelines will assist applicants to prepare applications to register medicinal products for human use in East Africa Partner States. The format for applications is the Common Technical Document (CTD).

These guidelines apply to MA applications for medicinal 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 approval should be within 12 months.

1.1 Comprehensive table of contents for all modules

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.

1.2 Cover letter

Applicants should include a cover letter 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 (Refer **Annex I**).

1.3 Application form

An application to register a medicinal 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.

1.4 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 EAC, a draft document may be included. The

approved SmPC from SDRA should then be supplied to the EAC-NMRA as they become available.

1.4.1 Prescribing information (Summary of Product Characteristics)

All prescription medicines should be accompanied by SmPC. *Refer EAC Guidelines on Summary of Products Characteristics for guidance on preparation of SmPC.*

1.4.2 Container labelling

Product should be labeled as prescribed in the *EAC Guidelines on container labeling for guidance on preparation of product labeling.*

1.4.3 Patient information leaflet (PIL)

All medicinal 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 labeling should be clearly expressed in English and French.

Refer EAC Guidelines on PIL for guidance on preparation of PIL.

1.4.4 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 Module1.4.4.

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 EAC-NMRA, during the evaluation process and prior to finalization of the application.

1.5 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 Information Summary
- 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 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 declaration form is provided as **Annex III.**

Additionally, a filled in Quality Information Summary as provided under **Annex IV** should be submitted.

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

If a 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 or Letter of Access to EAC-APIMF* as appropriate from API manufacturer. These letters should be included in Module 1.7. (Refer **Annex V and Annex VI**)

1.7 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 EAC GMP guidelines. Attacha WHO-typecertificateofGMP. For more information on GMP requirements and application for GMP inspection, refer *EAC Guidelines on Good Manufacturing Practice for more guidance.*

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

1.8 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

1.9 Regulatory status

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

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

1.9.2 Registration status in EAC Partner States

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

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

The applicant should provide, in Module 1.9.1 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.

1.9.4 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 in EAC. If the medicine has been rejected, repeatedly deferred, withdrawn or suspended then reasons must be stated. If rejection occurs during the EAC evaluation process, the EAC-NMRA should be informed.

1.10 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.

1.11 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.

1.12 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 in EAC region 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 **Annex VII** *following the guidance below.*

The Quality Information Summary as provided under **Annex IV** should also be provided.

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. Conclusions 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.

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.

Annex Iof the EAC Guideline on the Bioequivalence 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 EAC Guideline on Therapeutic Equivalence Requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance.

2.7.2 Summary of Clinical Pharmacology Studies

Refer the EAC Guideline on Therapeutic equivalence requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance.

2.7.3 Summary of Clinical Efficacy

Refer the EAC Guideline on Therapeutic equivalence requirements: Presentation of Biopharmaceutical and Bio-analytical Data for more guidance.

2.7.4 Summary of Clinical Safety

Refer the EAC Guideline 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 EAC in the order of preference in one of the following four options:

a) Option1: Certificate of suitability of European Pharmacopeia(CEP);
b) Option 2: Active pharmaceutical ingredient pre-qualified by WHO;
c) Option 3: EAC Active Pharmaceutical Ingredient Master File (EAC-APIMF);
d) Option 4: Full details in the Product Dossier (PD);

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 **(**Refer **Annex V).** Letter of access should be included in Module 1.7.

Where reference is made to EAC-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 EAC-NMRA. Applicant should provide the *Letter of Access to EAC-APIMF,* as appropriate from API manufacturer **(**Refer **Annex VI).** 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 EAC-NMRA 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: 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 to the EAC who refers to the CEP.

In addition, a written commitment should be included that the applicant will inform EAC 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.

b) Option 2: Active pharmaceutical ingredient pre-qualified by WHO

A complete copy of the Confirmation of API prequalification document should be provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.

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.

c) Option 3: EAC Active Pharmaceutical Ingredient Master File (EAC-APIMF)

i. Option 3 (a): A copy of confirmation of registration of the API by EAC NMRAs provided in Module 1, together with the duly filled out authorization box in the name of the FPP manufacturer or applicant.

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

- 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.

- 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.

- 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.

- 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.

- 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.

- 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.

- 3.2.S.5 Reference standards or materials – information on the FPP

manufacturer's reference standards.

- 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 API approved by the NMRAs.

ii. Option 3 (b): 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 EAC 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.

d) Option 4: 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 EAC Guidelines on Stability Requirements for Testing Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products (FPPs)

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:

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.

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 **(See Annex VIII)**

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 VIII).**

Refer FDA Guidance for Industry Process Validation: General Principles and Practices for more guidance at:- http://www.fda.gov/ downloads/Drugs/... /Guidances/ UCM070336. pdf

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 ICH Q2 for more guidance.

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 ICH Q2 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.

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.

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.

3.2.P.8.1 Stability Summary and Conclusion

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

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

3.2.P.8.3 Stability Data

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

Refer EAC 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.

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 EAC- National Medicines Regulatory Authorities.

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 guideline 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

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

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.

Refer ICH guidelines for the structure and content of clinical study report (E3).

5.3.1 Reports of Biopharmaceutics Studies

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

For Generic product

Refer EAC Guidelines on Therapeutic Equivalence Requirements.

5.3.1.3 *In vitro-In vivo* Correlation Study Reports

For Generic product

Refer EAC Guidelines on Therapeutic Equivalence Requirements.

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

For Generic product

Refer EAC 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 EAC Guidelines on Therapeutic Equivalence Requirements and bio-wavers.

5.4 Literature References

Refer list of the ICH guidelines on clinical studies