MEDICINES CONTROL AGENCY

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Guidance for the Application in the Common Technical Document (CTD) Format

1 INTRODUCTION

1.1. A Common Technical Document (CTD) is an internationally agreed upon format for the organisation and preparation of application dossiers for marketing authorization.

1.2. The document is based on the *International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use* (ICH) guidelines (ICH M4, ICH M4Q, ICH M4S, and ICH M4E).

1.1 PURPOSE AND SCOPE

1.1.1. This document provides guidance for the preparation of a product dossier in the CTD format for the Registration of Medicines for Human Use in The Gambia.

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

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

2 GENERAL PRINCIPLES OF PRESENTATION

2.1. Some headings and/or subheadings may not be applicable for certain dossiers, such as those for multisource (generic) medicines or variations. When no information is required in a specific section or subsection, that heading or subheading should be omitted or an explanation such as "not applicable" or "no study conducted" stated when no report or information is available for a section or subsection. The numbering of an omitted section should not be reused for another section.

Language

2.2. Applications for products seeking a region-wide market authorization shall be submitted in English.

2.3. In cases where there is the need to translate a document from its original language into English, the accuracy of the translations is the responsibility of the applicant. Translations of certificates shall be notarised.

Data Presentation

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

2.5. All pages shall be numbered appropriately with the format 'page x of y' to facilitate easy reference by evaluators.

2.6. Acronyms and abbreviation should be defined the first time they are used in each module.

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

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

3 STRUCTURE OF THE CTD FORMAT

Information within the CTD is organised into a series of structured documents which are in turn organised into modules as indicated below:

Number	Title and Main Section Headings
	Module 1: Administrative and Product Information
1.0	Table of Contents (Modules 1 to 5)
1.1	Correspondence
1.2	Administrative Information
1.3	Product Information
1.A	Appendix
	Module 2: Common Technical Document (CTD) Summaries
2.1	CTD Table of Contents (Modules 2 to 5)
2.2	CTD Introduction
2.3	Quality Overall Summary
2.4	Nonclinical Overview
2.5	Clinical Overview
2.6	Nonclinical Written and Tabulated Summaries
2.7	Clinical Summary
	Module 3: Quality
3.1	Table of Contents of Module 3
3.2	Body of Data
3.3	Literature References

	Module 4: Nonclinical Study Reports
4.1	Table of Contents of Module 4
4.2	Study Reports
4.3	Literature References
	Module 5: Clinical Study Reports
5.1	Table of Contents of Module 5
5.2	Tabular Listing of All Clinical Studies
5.3	Clinical Study Reports
5.4	Literature References
Red text indicates sections that are not normally needed for a generic drug	

Module 1: Administrative and Product Information

1.0 Table of Contents (ToC)

- List all documents included in Modules 1-5. **1.1Correspondence**
- Scientific information is not to be included in this Module.

1.1.1 Cover Letter

- The cover letter should clearly state what is being submitted
- Any cross-referenced regulatory document should be clearly stated in the cover letter
- Name of Applicant and Manufacturer
- Products with brand and generic name, dosage form and presentation
- Number of samples submitted

1.1.2 Copy of Correspondence Issued by the Regulatory Authority (RA)

- A copy of the correspondence issued by the RA, being responded to, where applicable (e.g. request for additional information).

1.1.3 Information Solicited by the Regulatory Authority

- Responses to requests by the RA are to be provided in Question and Answer format, where applicable.
- Supporting data is to be placed in the appropriate Module of the regulatory document and cross-referenced here.

1.1.4 Meeting Information

- Any meeting related information and documentation, with the exception of an Appeal meeting, where applicable

1.1.5 Request for Appeal Documentation

- Any documentation required as part of a Request to Appeal a regulatory decision.

1.1.6 General Note to Reviewer

- The Note to Reviewer should be used to facilitate the review, for example to identify changes in a section and/or document.

1.2 Administrative Information

1.2.1 Application Forms

- Completed and signed application forms.

1.2.2 Fee Forms

- Proof/evidence of payment.

1.2.3 Certification and Attestation Forms

- Completed and signed forms, as applicable (e.g. Certification of Suitability to the Monographs of the Pharmacopoeia, WHO Organization Confirmation of Prequalification (WHO-CPQ), Certificate of Pharmaceutical Product (CPP), all Certificates of analysis as required in the quality guidance, Market Authorisation or the Product Certificate issued by the RA, etc).

1.2.4 Compliance and Site Information

- GMP compliance information.
- Regulatory GMP compliance status issued by other jurisdictions, including Date of last GMP and/or pre-approval inspection, and any observation-related information.
- Any other regulatory compliance and site-related information which is not currently mentioned.

1.2.5 Authorization for Sharing Information

- Letters authorising the RA to access Drug Master Files (DMFs)/ active pharmaceutical ingredient master files or Site Reference files (SRF).

1.2.6 Regional and International Regulatory Status

- Provide evidence on registration status of the proposed product(s) and, approved indications in the country of origin and in other countries/regions.
- Provide evidence if the API or Finished Pharmaceutical Product is prequalified by the WHO.
- International / regional registration, review and/or marketing status, including date of filing, approval of product or supplemental changes in other jurisdictions, information regarding the withdrawal, stop of sale and/or market recall.
- Certification issued by the competent authority for the country of product origin that the product is marketed in the country of origin.

1.2.7 Post-Authorization Information

- Periodic Safety Update Reports (PSURs), as applicable.

1.2.8 Other Administrative Information

- This section is for any administrative information that does not have a designated location in the CTD format.

1.3 Product information

1.3.1 Summary of Product Characteristics (Prescribing Information)

- A copy of the Summary of Product Characteristics (SmPC) in English.

1.3.2 Patient Information Leaflet

- A copy of the Package Insert/Patient Information Leaflet (PIL).

1.3.3 Container Labels

- All container labels, including the labels for all strengths, dosage forms and reconstitution diluents, where applicable.

1.3.4 Foreign Labelling

- SmPC approved for WHO prequalified products and those marketed elsewhere in any African regions in English.

1.3.5 Reference Product Labelling

- For multisource (generic) products, the SmPC for the Reference Product(s).

1.A Appendix

Module 1.A.1 Electronic Documents

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

Module 2: CTD Summaries

2.1 CTD Table of Contents (Module 2-5)

- List all documents included in Modules 2-5.

2.2 CTD Introduction

- Include proprietary name, non-proprietary name or common name of the active pharmaceutical ingredient (API), company name, dosage form(s), strength(s), route(s) of administration, and proposed indication(s).
- Describe briefly the contents of the Modules 2 to 5 with appropriate cross-references to them.

2.3 Quality Overall Summary (QOS)

- The QOS should follow the scope and the outline of the Body of Data in Module 3.

Ref: ICH M4Q(R1)

2.3.S Drug Substance (Active Pharmaceutical Ingredient)

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

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

- Include information from Module 3.2.S.1

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

- Include information from Module 3.2.S.2
- Provide the name, address and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing.
- A brief description of the manufacturing process (including, for example, reference to starting materials, critical steps, and reprocessing) and the controls that are intended to result in the routine and consistent production of material(s) of appropriate quality.
- A flow diagram, as provided in 3.2.S.2.2.
- A description of the Source and Starting Material and raw materials of biological origin used in the manufacture of the API, as described in 3.2.S.2.3
- Highlight critical process intermediates, as described in 3.2.S.2.4
- A description of process validation and/or evaluation, as described in 3.2.S.2.5.

2.3.S.3 Characterisation (name, manufacturer)

- A summary of the interpretation of evidence of structure and isomerism, as described in 3.2.S.3.1.
- A tabulated summary of the data provided in 3.2.S.3.2, with graphical representation, where appropriate

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

- A brief summary of the justification of the specification(s), the analytical procedures, and validation.
- Specification from 3.2.S.4.1
- A tabulated summary of the batch analyses from 3.2.S.4.4, with graphical representation where appropriate.

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

- Information from 3.2.S.5 (tabulated presentation, where appropriate).

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

- A brief description and discussion of the information from 3.2.S.6.

2.3.S.7 Stability (name, manufacturer)

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

2.3.P Finished Pharmaceutical Product

2.3.P.1 Description and Composition of the Medicine

- Information from 3.2.P.1.
- Composition from 3.2.P.1.

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

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

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

- Information from 3.2.P.3 including
  - Information on the manufacturer
  - A brief description of the manufacturing process and the controls that are intended to result in the routine and consistent production of product of appropriate quality
  - A flow diagram, as provided under 3.2.P.3.3
  - A brief description of the process validation and/or evaluation, as described in 3.2.P.3.5

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

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

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

- A brief summary of the justification of the specification(s), a summary of the analytical procedures and validation, and characterisation of impurities should be provided.
- Specification(s) from 3.2.P.5.1
- A tabulated summary of the batch analyses provided under 3.2.P.5.4, with graphical representation where appropriate

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

- Information from 3.2.P.6 (tabulated presentation, where appropriate).

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

- A brief description and discussion of the information in 3.2.P

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

- A summary of the studies undertaken (conditions, batches, analytical procedures) and a brief discussion of the results and conclusions of the stability studies and analysis of data.
- Conclusions with respect to storage conditions and shelf-life and, if applicable, in-use storage conditions and shelf-life should be given.
- A tabulated summary of the stability results from 3.2.P.8.3, with graphical representation where appropriate
- The post-approval stability protocol, as described in 3.2.P.8.2

2.3.A Appendices

2.3.R Regional Information

2.4 Non-Clinical Overview (not required for generic medicines)

- The Nonclinical Overview should provide an integrated overall analysis of the information in the Module 4 (not more than 30 pages).
- The Nonclinical Overview should be presented in the following sequence:
  - Overview of the nonclinical testing strategy
  - Pharmacology
  - Pharmacokinetics
  - Toxicology
  - Integrated overview and conclusions
  - List of literature references
- 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.

2.5 Clinical Overview

- The Clinical Overview is intended to provide a critical analysis of the clinical data.
- Provide a succinct discussion and interpretation of the clinical information together with any other relevant information (e.g., pertinent animal data or product quality issues that may have clinical implications).
- The clinical overview should be presented in the following order:
  - Table of Contents

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

Ref: ICH M4E(R1) Module 2.5

Module 3: Quality

3.1 Table of Contents (Module 3)

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

3.2.S Body of Data - Drug Substance (API)

- The following information may be submitted as information for the API as applicable:
  - Option 1 - Full details in the product dossier
  - Option 2 – Confirmation that Drug Substance (API) is pre-qualified by the WHO
  - Option 3 - A Certificate of Suitability of applicable Pharmacopeia e.g. European Pharmacopeia (CEP).
- For a medicine containing more than one API, the information should be submitted for each API.
- Evidence of WHO Pre-qualification should be provided in Module 1.2.6, where applicable.

Ref: WHO Technical Report Series, No. 970 Annex 4

	Option 2 API-PQP by WHO	Option 3 CEP
3.2.S.1.3 General properties	Yes	Yes
3.2.S.1 Manufacture		
3.2.S.2.1 Manufacturer	Yes if sterility of FPP depends on sterile API	
3.2.S.2.2 Description of manufacturing process and process controls		
3.2.S.2.3 Control of materials		
3.2.S.2.4 Controls of critical steps and intermediates		
3.2.S.2.5 Process validation and/or Evaluation		
3.2.S.2.6 Manufacturing Process development		
3.2.S.3.1 Elucidation of structure and other	Yes	Yes

	Option 2 API-PQP by WHO	Option 3 CEP
3.2.S.4 Control of Drug Substance		
3.2.S.4.1 Specification	Yes	Yes
3.2.S.4.2 Analytical procedures and validation	Yes	Yes
3.2.S.4.3 Validation of Analytical Procedures	Yes	Yes
3.2.S.4.4 Batch analysis	Yes	Yes
3.2.S.5 Reference standards or materials	Yes	Yes
3.2.S.6 Container-closure system		Yes
3.2.S.7 Stability		
3.2.S.7.1 Stability Summary and Conclusion	Yes If longer retest period or higher storage temperatures than the prequalified API	Yes If longer retest period or higher storage temperatures than the prequalified API
3.2.S.7.2 Post-approval stability Protocol and stability commitment		
3.2.S.7.3 Stability Data		

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

3.2.S.1.1 Nomenclature (name, manufacturer)

- Information on the nomenclature of the drug substance should be provided. For example:
  - Recommended International Non-proprietary Name (INN);
  - Compendial name if relevant;
  - Chemical name(s);
  - Company or laboratory code;
  - Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN), and
  - Chemical Abstracts Service (CAS) registry number.

3.2.S.1.2 Structure (name, manufacturer)

- The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass.

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

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

Ref: ICH Q6A and Q6B

3.2.S.2 Manufacturer (name, manufacturer)

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

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

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

- Description of the manufacturing process and the summary diagram of the active substance.
- Information should be provided to adequately describe the manufacturing process and process control; for example, a flow diagram of the synthetic process(es) that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, and identified operating conditions and solvents.
- Reprocessing steps should be identified and justified and any data to support this justification should be referenced.

3.2.S.2.3 Control of Materials (name, manufacturer)

- Materials used in the manufacture of the drug substance (e.g., raw materials, starting materials, solvents, reagents, catalysts) should be listed identifying where each material is used in the process.
- Information on the quality and control of these materials should be provided.

Ref: ICH Q5A, Q5B, and Q6B

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

- Critical Steps: Tests and acceptance criteria (with justification including experimental data) performed at critical steps identified in 3.2.S.2.2 of the manufacturing process to ensure that the process is controlled.
- Intermediates: Information on the quality and control of intermediates isolated during the process

Ref: ICH Q6A and Q6B

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

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

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

- A description and discussion should be provided of the significant changes made to the manufacturing process and/or manufacturing site of the drug substance used in producing non-clinical, stability, scale-up, pilot, and , if available, production scale batches.
- Reference should be made to the drug substance data provided in section 3.2.S.4.4.

Ref: ICH Q3A

3.2.S.3 Characterisation (name, manufacturer)

- Describe the method of Characterization

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

- Confirmation of structure based on e.g. Synthetic route and spectral analyses should be provided including information such as the potential for isomerism, the identification of stereochemistry, or the potential for forming polymorphs.

Ref: ICH Q6A

3.2.S.3.2 Impurities (name, manufacturer)

- Information on impurities.

Ref: ICH Q3A, Q3C, Q5C, Q6A, and Q6B

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

3.2.S.4.1 Specification (name, manufacturer)

- The specification for the drug substance.

Ref: ICH Q2(R1), Q6B and WHO Technical Report Series, No. 970-Annex 4

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

- The analytical procedures used for testing the drug substance.

Ref: ICH Q2(R1)

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

- Analytical validation information, including experimental data for the analytical procedures used for testing the drug substance.

Ref: ICH Q2(R1) and Q6B

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

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

Ref: ICH Q3A, Q3C, Q6A, and Q6B

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

- Justification for the drug substance specification.

Ref: ICH Q3A, Q3C, Q6A and Q6B

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

- Information on the reference standards or reference materials used for testing of the drug substance.

Ref: ICH Q6A and Q6B

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

- A description of the container closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non–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 drug substance, including sorption to container and leaching, and/or safety of materials of construction.
- Provide a certificate of analysis for the container closure materials in module 1.2.3

Ref: WHO Technical Report Series, No. 902 Annex 9

3.2.S.7 Stability (name, manufacturer)

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

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

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

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

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

Ref: ICH Q1A (20), Q1B (22), Q1D (24), Q1E (23), and WHO Technical Report Series, No. 953, Annex 2

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

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

Ref: ICH Q1A, Q1B, Q1D, Q1E, Q2(R1), and WHO Technical Report Series, No. 953, Annex 2

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

3.2.P.1 Description and Composition of the Medicine (name, dosage form)

- A description of the medicine (Finished Pharmaceutical Product – FPP) and its composition, including for example:
  - A description of the dosage form;
  - Composition e.g. list of all components of the dosage form, and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturers specifications);
  - Description of accompanying reconstitution diluent(s); and
  - Type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.
- **Note:** For a product supplied with reconstitution diluents(s) the information on the diluent(s) should be provided in a separate part

"P" as appropriate.

Ref: ICH Q6A and Q6B

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

- The Pharmaceutical development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container-closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the product dossier.
- 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.

Ref: ICH Q6A, Q6B, and WHO Technical Report Series, No. 970, Annex 4

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

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

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

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

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

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

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

- A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage.
- The differences between clinical formulations and the formulation (e.g. composition) described should be discussed.
- Results from comparative *in-vitro* studies (e.g. dissolution) or comparative *in- vivo* studies (e.g. Bioequivalence) should be discussed when appropriate.

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

- Any overages in the formulations(s) should be justified.

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

3.2.P.2.3 Manufacturing Process Development (name, dosage form)

- The selection and optimization of the manufacturing process

described in 3.2.P.3.3, in particular its critical aspects, should be explained.

- Where relevant, the method of sterilization should be explained and justified.
- Differences between the manufacturing processes used to produce pivotal clinical batches and the process described that can influence the performance of product should be discussed.

3.2.P.2.4 Container Closure System (name, dosage form)

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

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

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

3.2.P.2.6 Compatibility (name, dosage form)

- The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g. precipitation of API in solution, adsorption on injection vessels) stability should be addressed to provide appropriate and supportive information for the labelling.

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

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

- The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided. Include, for example, production, sterilization, packaging and quality control.
- For each site where the major production step(s) is/are carried out, attach (in module 1.2.6) a valid manufacturing authorization for pharmaceutical production.
- Attach an original WHO-type certificate of GMP issued by the competent authority.

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

- A recent batch formula should be provide that includes a list of 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.

3.2.P.3.3 Description of Manufacturing Process and Process Controls (name, dosage form)

- A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.
- A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided.
- Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should at least, be identified by type (e.g. tumble blend, in-line homogenizer) and working capacity, where relevant.
- Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH.
- Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified in section 3.2.P.3.4.
- In certain case, environmental conditions (e.g. experimentally documented temperature and relative humidity for hygroscopic FPPs) should be stated.
- Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section.

Ref: ICH Q6B

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

- **Critical steps:** Test and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps of the manufacturing process, to ensure that the process is controlled.
- **Intermediates:** Information on the quality and control of intermediates isolated during the process should be provided.

Ref: ICH Q2(R1), Q6A, and Q6B

3.2.P.3.5 Process Validation and/or Evaluation (name, dosage form)

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

Ref: ICH Q6B

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

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

- The specifications for excipients should be provided.

Ref: ICH Q6A and Q6B

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

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

Ref: ICH ICH Q2(R1)

3.2.P.4.3 Validation of Analytical Procedures (name, dosage form)

- Analytical validation information, including experimental data, for the analytical procedures used for testing the excipients should be provided, where appropriate.

Ref: ICH Q6B and Q2(R1)

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

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

Ref: ICH Q3C and Q6B

3.2.P.4.5 Excipients of Human or Animal Origin (name, dosage form)

- For excipients of human or animal origin information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed and viral safety data. (Details in 3.2.A.2).

Ref: ICH Q5A, Q5D, and Q6B

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

- For excipient(s) used for the first time in an FPP or by a new route of administration, full details of manufacture, characterization, and controls, with cross-references to supporting safety data (non-clinical and/or clinical) should be provided according to the API and/or FPP format. (Details in 3.2.A.3).

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

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

- The specification(s) for the drug product.

Ref: ICH Q3B, Q6A and Q6B

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

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

- The analytical procedures used for testing the FPP.

Ref: ICH Q2(R1) and Q6B

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

- Analytical validation information, including experimental data, for the analytical procedures used for testing the FPP.

Ref: ICH Q2(R1) and Q6B

3.2.P.5.4 Batch Analyses

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

Ref: ICH Q3B, Q3C, Q6A, and Q6B

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

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

Ref: ICH Q3B, Q5C, Q6A, and Q6B

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

- Justification for the proposed drug product specification(s).

Ref: ICH Q3B, Q6A, and Q6B

3.2. P.6 Reference Standards or Materials (name, dosage form)

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

Ref: ICH Q6A and Q6B

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

- A description of the container closure system should be provided, including the identity of materials of construction of each primary packaging component and its specification.
- The specifications should include description and identification (and critical dimensions, with drawings, where appropriate)).
- Non-compendial methods (with validation) should be included where appropriate.
- For non- functional secondary packaging components (e.g., those that neither provide additional protection nor serve to deliver the product), only a brief description should be provided.
- For functional secondary packaging components, additional information should be provided.
- The suitability of the container closure system used for the storage, transportation (shipping) and use of the FPP should be discussed and located in 3.2.P.2.

Ref: WHO Technical Report Series, No. 902 Annex 9

- Officially recognized pharmacopoeias should be consulted for recommendations on the packaging information for FPPs.

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

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

3.2. P.8.1 Stability Summary and Conclusions (name, dosage form)

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

Ref: ICH Q1A, Q1B, Q3B, Q5C, Q6A, and WHO Technical Report Series, No. 953 Annex 2

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

- The post-approval stability protocol and stability commitment

Ref: ICH Q1A and Q5C

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

- Results of the stability studies should be presented in an appropriate format (e.g., tabular, graphical and narrative). Information on the analytical procedures used to generate the data and validation of these procedures should be included.
- Information on characterisation of impurities is located in 3.2.P.5.5.

Ref: ICH Q1A, Q1B, Q2(R1) and Q5C

3.2. A Appendices (name, dosage form)

3.2. R Regional Information (name, dosage form)

3.3 Literature References (name, dosage form)

- Key literature referenced should be provided, if applicable.

Module 4: Non-Clinical Summaries (normally not required for generic medicines)

- This module deals with the toxicity testing intended to justify the stability and safety of the product.

Ref: ICH M4S(R2)

4.1 Table of Contents (Module 4)

4.2 Study Reports

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

4.2.1.2 Secondary Pharmacodynamics

4.2.1.3 Safety Pharmacology

4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4 2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)

4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology

4.2.3.1 Single-Dose Toxicity (in order by species, by route)

4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)

4.2.3.3 Genotoxicity

4.2.3.3.1 In vitro

4.2.3.3.2 In vivo (supportive toxicokinetics evaluations)

4.2.3.4 Carcinogenicity (including supportive toxicokinetics evaluations)

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

4.2.3.4.2 Short- or medium-term studies (including range-finding studies that cannot appropriately be included under repeat-dose toxicity or pharmacokinetics)

4.2.3.4.3 Other studies

4.2.3.5 Reproductive and Developmental Toxicity

4.2.3.5.1 Fertility and early embryonic development

4.2.3.5.2 Embryo-fetal development

4.2.3.5.3 Prenatal and postnatal development, including maternal function

4.2.3.5.4 Studies in which the offspring (juvenile animals) are dosed and/or further evaluated.

4.2.3.6 Local Tolerance

4.2.3.7 Other Toxicity Studies (if available)

4.2.3.7.1 Antigenicity

4.2.3.7.2 Immunotoxicity

4.2.3.7.3 Mechanistic studies (if not included elsewhere)

4.2.3.7.4 Dependence

4.2.3.7.5 Metabolites

4.2.3.7.6 Impurities

4.2.3.7.7 Other

4.3 Literature References

Module 5: Clinical Summaries (for generic medicines normally only *Module 5.3* is required).

- Module 5 provides the recommended organization for the placement of clinical study reports and related information. The placement of a report should be determined by the primary objective of the study.
- Each study report should appear in only one section. Where there are multiple objectives, the study should be cross-referenced in the various sections.

Ref: ICH M4E(R2)

5.1 Table of Contents (Module 5)

5.2 Tabular Listing of Clinical Studies

5.3 Clinical Study Reports

5.3.1 Reports of Bio-pharmaceutic Studies

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

- When the primary purpose of a study is to assess the PK of a drug, but also includes BA information, the study report should be submitted in Section 5.3.1, and referenced in Sections 5.3.1.1 and/or 5.3.1.2.

5.3.1.1 Bioavailability (BA) Study Reports

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

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

- Studies in this section compare the rate and extent of release of the drug substance from similar drug products (e.g. tablet to tablet, tablet to capsule).
- Comparative BA or BE studies may include comparisons between
  - the drug product used in clinical studies supporting effectiveness and the to-be-marketed drug product,
  - the drug product used in clinical studies supporting effectiveness and the drug product used in stability batches, and
  - similar drug products from different manufacturers

5.3.1.3 In vitro-In vivo Correlation Study Reports

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

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

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

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using Other Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

5.3.3.2 Patient PK and Initial Tolerability Study Reports

5.3.3.3 Intrinsic Factor PK Study Reports

5.3.3.4 Extrinsic Factor PK Study Reports

5.3.3.5 Population PK Study Reports

5.3.4 Reports of Human Pharmacodynamic Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

5.3.4.2 Patient PD and PK/PD Study Reports

5.3.5 Reports of Efficacy and Safety Studies

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

5.3.5.2 Study Reports of Uncontrolled Clinical Studies References

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

5.3.5.4 Other Clinical Study Reports

5.3.6 Reports of Post-marketing Experience

- For products that are currently marketed, reports that summarise marketing experience (including all significant safety observations) should be included.

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

5.4 Literature References

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

4 REFERENCES

ICH Common Technical Document References (http://www.ich.org)

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

ICH Quality Guidelines

1. ICH Q1A(R2) - Stability Testing of New Drug Substances and Products (2003)
2. ICH Q1B Stability Testing: Photostability Testing of New Drug Substances and Products (1996)

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

World Health Organization Guidelines

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

World Health Organization Templates
[https://extranet.who.int/prequal/content/who-medicines-prequalification-guidance]