Guideline

Egyptian Guidelines on CTD Quality Module for Human Pharmaceuticals

Year 2023

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Contents

1. Introduction

- This guidance aims to provide applicants with information and documents required for preparation of the CTD Quality Module for human pharmaceutical products.
- It aims also to inform the applicants with the adopted references and guidelines used in the evaluation of CTD Quality Module in a way that does not contradict with any of the Egyptian published regulations, legislations, decisions & registration ministerial decrees.
- It should be noted that the Egyptian Drug Authority has the right to request any additional information or documents and refer to any other international guidelines that aren't listed in this guidance, in order to establish the safety, efficacy and quality of a medicine in keeping with the knowledge current at the time of evaluation, alternative approaches may be used but these should be scientifically and technically justified.

2. Scope

This guidance applies for any human pharmaceutical product submitted for evaluation of CTD Quality Module according to different Ministerial Decrees and Technical Committee Decisions.

3. Definitions

3.1. The Common Technical Document (CTD): is a set of specifications for a dossier to be submitted to the regulatory authorities for the registration/marketing authorization of medicines.

3.2. The International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH): is unique in bringing together the regulatory authorities and pharmaceutical industry to discuss scientific and technical aspects of pharmaceuticals and develop ICH guidelines.

3.3. The Certification of Suitability (CEP): It is a certificate to certify that the quality of the substance produced at the site(s) listed on the CEP (or its annexes) is suitably controlled by the corresponding Ph. Eur. monograph (current edition including supplements), supplemented by the test(s) stated on the CEP and the analytical procedures included in the annex.

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

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

3.6. API Master file (APIMF)_: other global terms include DMF (drug master file) and ASMF (active substance master file) is a document containing complete information on an Active Pharmaceutical Ingredient (API) containing factual and complete information on a drug product's chemistry, manufacture, stability, purity, impurity profile, packaging, and the cGMP status of any human drug product. A drug master file comprises two parts: the Applicant's Part (Open Part), which contains all the information that the license-holder needs to assess the quality and submit a license or amendment application; and the Restricted Part (Closed Part), which contains confidential information about the manufacturing procedure only disclosed to the authorities.

3.7. Applicant: The person or company who submits an application for marketing authorization of a new pharmaceutical product, an update to an existing marketing authorization or a variation to an existing market authorization.

3.8. 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.

3.9. API Intermediate: A material produced during steps of the processing of an API that undergoes further molecular change or purification before it becomes an API. Intermediates may or may not be isolated (5). manufacturer. A company that carries out operations such as production, packaging, repackaging, labelling and relabeling of pharmaceuticals.

3.10. 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.

3.11. 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.

3.12. 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.

4. Procedures

4.1 Module 3. Quality:

The CTD is organized into five modules. Module 1 is region specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guidance should ensure that Modules 2 through 5 are provided in a format acceptable to the regulatory authorities.

4.1.1 Information on Quality should be presented in the structured CTD format described in the ICH M4Q guidance as follow:

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3.3 Literature References

Reference:

- ICH guideline M4 (R4) on common technical document (CTD) for the registration of pharmaceuticals for human use - organization of CTD

4.1.2 Description of content of Module 3

3.1 Table of contents

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

3.2 Body of Data

3.2.S DRUG SUBSTANCE

3.2.S.1 General Information

3.2.S.1.1 Nomenclature

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

- Recommended International Nonproprietary 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)
- Chemical Abstracts Service (CAS) registry number.

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.

3.2.S.1.3 General Properties

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

3.2.S.2 Manufacture

3.2.S.2.1 Manufacturer(s)

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.

3.2.S.2.2 Description of Manufacturing Process and Process Controls

Information should be provided to adequately describe the manufacturing process and process controls of the drug substance.

A flow diagram of the synthetic process(es) should be provided that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance 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.

3.2.S.2.3 Control of Materials

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.

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.

3.2.S.2.5 Process Validation and/or Evaluation

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

3.2.S.2.6 Manufacturing Process Development

A description and discussion should be provided for the drug substances development.

References:

- Investigation of chiral active substances (human) - Scientific guideline.
- Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11

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.

3.2.S.3.2 Impurities

Information on impurities should be provided.

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification

The specification for the drug substance should be provided.

References:

- ICH Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances.
- ICH Q3A (R2) Impurities in new drug substances - Scientific guideline.
- ICH Q3C (R8) Residual solvents - Scientific guideline.
- ICH Q3D Elemental impurities - Scientific guideline - Scientific guideline.
- ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - Scientific guideline
- Setting specifications for related impurities in antibiotics.

3.2.S.4.2 Analytical Procedures

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

References:

- ICH Q2(R2) Validation of analytical procedures - Scientific guideline

3.2.S.4.3 Validation of Analytical Procedures

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

References:

- ICH Q2(R2) Validation of analytical procedures - Scientific guideline

3.2.S.4.4 Batch Analyses

Description of batches (batch number, type, manufacturing date & production site) and results of batch analyses should be provided.

3.2.S.4.5 Justification of Specification

Justification for the drug substance specification should be provided.

3.2.S.5 Reference Standards or Materials

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

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).

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.

References:

- WHO TRS 986 - annex 6 "Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part".
- Container closure systems for packaging human drugs and biologics (FDA Guidance for Industry, May 1999).

3.2.S.7 Stability

3.2.S.7.1 Stability Summary and Conclusions

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.

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment

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

3.2.S.7.3 Stability Data

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

References:

- ICH Q1A: "Stability testing of new drug substances and drug products".
- ICH Q1B: "Photo stability Testing of New Drug Substances and Products"
- ICH Q1D: "ICH Q1D Bracketing and matrixing designs for stability testing of drug substances and drug products.
- ICH Q1E: "Evaluation for stability data"
- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products WHO technical series 1010, 2018 annex 10.
- WHO Technical Report Series, No. 929, Annex 5, 2005, Table A.1 (7) "A typical set of studies of the degradation paths of an active pharmaceutical ingredient".
- Declaration of storage conditions for medicinal products particulars and active substances (Annex)

➢ Active Pharmaceutical Ingredients (API) Mixtures

"API mix" is defined as a mixture of an API (active pharmaceutical ingredient) with one or more excipients. Typical examples are the addition of an antioxidant to an API, or the introduction of an API into a matrix.

References:

- Quality Working Party questions and answers on API mix

➢ Options for S-part submission

The applicant should clearly indicate at the beginning of the API section how the information on the API for each API manufacturer is being submitted:

- Option 1: Confirmation of API prequalification document.
- Option 2: Certificate of suitability of the European Pharmacopoeia (CEP).
- Option 3: API master file (APIMF/DMF).
- Option 4: Full details in the Product Dossier.

➢ In case of Option 2: Certificate of Suitability of the European Pharmacopoeia (CEP).

A complete copy of the CEP (including any annexes) should be provided in this section. The CEP holder on behalf of the FPP manufacturer or applicant who refers to the CEP should duly fill out the declaration of access for the CEP to applicant/FPP manufacturer.

In addition, a written commitment should be included that the applicant will inform EDA in the event of changes, or if the CEP is withdrawn. It should also be acknowledged by the applicant that withdrawal of the CEP would require additional consideration of the API data requirements (full Module 3.2.S) to support the product dossier.

The written commitment should accompany the copy of the CEP. Along with the CEP, the applicant should supply the following information in the dossier.

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.

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.

3.2.S.4.1 Specification

The specifications of the FPP manufacturer including all tests and limits of the CEP and Ph.Eur. monograph and any additional tests and acceptance criteria

that are not controlled in the CEP and Ph.Eur. monograph, such as polymorphs and/or particle size distribution.

3.2.S.4.2 / 3.2.S.4.3 Analytical procedures and validation

For any methods used by the FPP manufacturer in addition to those in the CEP and Ph.Eur. monograph.

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.6 Container closure system

Specifications including descriptions and identification of primary packaging components. Exception: where the CEP specifies a container closure system and the applicant / FPP manufacturer declares to use the same container closure system.

3.2.S.7 Stability

Exception: where the CEP specifies a re-test period that is the same as or of longer duration, and storage conditions which are the same or higher temperature and humidity as proposed by the applicant.

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

3.2.P DRUG PRODUCT

3.2.P.1 Description and Composition of the Drug Product

A description of the drug product and its composition should be provided. The information provided should include, for example:

• Description of the dosage form;

• Composition, i.e., list of all components of the dosage form, and their amount on a per unit basis (including overages, if any) the function of the components, and a reference to their quality standards (e.g., compendial monographs or manufacturer's specifications)

• Description of accompanying reconstitution diluent(s); and

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

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 application.

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 drug product quality.

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

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The compatibility of the drug substance 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 drug substance that can influence the performance of the drug product should be discussed. For combination products, the compatibility of drug substances with each other should be discussed.

3.2.P.2.1.2 Excipients

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

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

A brief summary describing the development of the drug product should be provided, taking into consideration the proposed route of administration and usage.

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

Any overages in the formulation(s) described in 3.2.P.1 should be justified.

3.2.P.2.2.3 Physicochemical and Biological Properties

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

3.2.P.2.3 Manufacturing Process Development

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.

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 drug product 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 drug product).

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.

3.2.P.2.6 Compatibility

The compatibility of the drug product with reconstitution diluent(s) or dosage devices (e.g., precipitation of drug substance in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labeling.

References:

- ICH Q8 (R2) Pharmaceutical development - Scientific guideline

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

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.

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.

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

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.

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).

References:

- Process validation for finished products – information and data to be provided in regulatory submissions
- Sterilization of the medicinal product, active substance, excipient and primary container

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

The specifications for excipients should be provided.

3.2.P.4.2 Analytical Procedures

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

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, where appropriate.

3.2.P.4.4 Justification of Specifications

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

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; viral safety data). (Details in 3.2.A.2).

3.2.P.4.6 Novel Excipients

For excipient(s) used for the first time in a drug product 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 drug substance format. (Details in 3.2.A.3).

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

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

References:

- ICH Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances
- Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (FDA Guidance for Industry, 2018)
- ICH Q3B (R2) Impurities in new drug products - Scientific guideline
- ICH Q3C (R8) Residual solvents - Scientific guideline
- ICH Q3D Elemental impurities - Scientific guideline - Scientific guideline
- ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - Scientific guideline
- Setting specifications for related impurities in antibiotics.
- Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action.

3.2.P.5.2 Analytical Procedures

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

References:

- ICH Q2(R2) Validation of analytical procedures - Scientific guideline

3.2.P.5.3 Validation of Analytical Procedures

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

References:

- ICH Q2(R2) Validation of analytical procedures - Scientific guideline

3.2.P.5.4 Batch Analyses

A description of batches (Type, batch number, strength, manufacturing date & site) and results of batch analyses should be provided.

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".

3.2.P.5.6 Justification of Specification(s)

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

3.2.P.6 Reference Standards or Materials

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

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).

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.

References:

- WHO TRS 986 - annex 6 “Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part”.
- Container closure systems for packaging human drugs and biologics (FDA Guidance for Industry, May 1999).

3.2.P.8 Stability

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

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

3.2.P.8.3 Stability Data

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

References:

- ICH Q1A: "Stability testing of new drug substances and drug products".
- ICH Q1B: "Photo stability Testing of New Drug Substances and Products"
- ICH Q1D: "ICH Q1D Bracketing and matrixing designs for stability testing of drug substances and drug products.
- ICH Q1E: "Evaluation for stability data"
- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products WHO technical series 1010, 2018 annex 10.
- Declaration of storage conditions for medicinal products particulars and active substances (Annex)
- In-use stability testing of human medicinal products

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Not Applicable

3.2.A.2 Adventitious Agents Safety Evaluation

- Adventitious agents are defined by the World Health Organization (WHO) as microorganisms that may have been unintentionally introduced into the manufacturing process of a biological medicinal product.
  - These include bacteria, fungi, mycoplasma/spiroplasma, mycobacteria, rickettsia, protozoa, parasites, transmissible spongiform encephalopathy (TSE) agents and viruses.
- Information assessing the risk with respect to potential contamination with adventitious agents should be provided in this section.

  This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

3.2.A.3 Excipients

- If a significant amount of data for an excipient (e.g., a novel excipient or a non-compendial non-novel excipient) needs to be provided, this information should be included in 3.2.A.3 Excipients, if required.

  If only a minimal amount of information was necessary for these excipients (e.g., pharmacopeia), this information should be provided in 3.2.P.4.1 and/or 3.2.P.2.1.2.
- **Novel Excipients** means a material or a composition that has not been previously used in an approved drug product or that has been previously used in an approved drug product but

which it is desired to employ for a new route of administration, or a higher level of use than has been previously listed in the IID or Handbook of pharmaceutical Excipients.
Full details of manufacture, characterisation and controls with cross references to supporting safety data should be provided for novel excipients, according to the drug substance format.

3.2.R Regional information

3.2.R.1 Production documents

3.2.R.1.1 Executed production documents

- The Pilot/Primary batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.
- Copies of the executed production documents should be provided for the batches used in the comparative bioavailability or biowaiver studies.
- English translations of executed records should be provided, where relevant

3.2.R.1.2 Master production documents

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

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

h) Precautions necessary to ensure product quality (e.g., temperature and humidity control, maximum holding times);
i) For sterile products, reference to SOPs in appropriate sections and a list of all relevant SOPs at the end of the document;
j) Theoretical and actual yield;

3.2.R.2 Analytical Procedures and Validation information

Summaries for the analytical procedures and validation information (in a tabular forms) from sections 3.2.S.4.2, 3.2.S.4.3, 2.3.S.4.4, 2.3.S.7.3, 3.2.P.5.2 and 3.2.P.5.3, where relevant.

3.3 Literature references

References to the scientific literature relating to both the API and FPP should be included in this section of the product dossier when appropriate.

4.2. Specific types of products

References:

- Pharmaceutical quality of inhalation and nasal products - Scientific guideline
- Quality of oral modified release products - Scientific guidelines.
- Pharmaceutical development of intravenous medicinal products containing active substances solubilized in micellar systems (non-polymeric surfactants) - Scientific guideline

5. References

1- The Common Technical Document for The Registration of Pharmaceuticals for Human Use: Quality – M4Q (R1).
2- ICH guideline M4 (R4) on common technical document (CTD) for the registration of pharmaceuticals for human use - organization of CTD
3- WHO TRS 986 - annex 6 “Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product: quality part”.
4- Investigation of chiral active substances (human) - Scientific guideline.
5- Development and Manufacture of Drug Substances (Chemical Entities and Biotechnological/Biological Entities) Q11
6- ICH Q6A specifications: test procedures and acceptance criteria for new drug substances and new drug products: chemical substances.
7- ICH Q3A (R2) Impurities in new drug substances - Scientific guideline.
8- ICH Q3C (R8) Residual solvents - Scientific guideline.
9- ICH Q3D Elemental impurities - Scientific guideline - Scientific guideline.
10- ICH M7 Assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk - Scientific guideline
11- Setting specifications for related impurities in antibiotics.

12- ICH Q2(R2) Validation of analytical procedures - Scientific guideline
13- Container closure systems for packaging human drugs and biologics (FDA Guidance for Industry, May 1999).
14- ICH Q1A: "Stability testing of new drug substances and drug products".
15- ICH Q1B: "Photo stability Testing of New Drug Substances and Products"
16- ICH Q1D: "ICH Q1D Bracketing and matrixing designs for stability testing of drug substances and drug products.
17- ICH Q1E: "Evaluation for stability data"
18- Stability testing of active pharmaceutical ingredients and finished pharmaceutical products WHO technical series 1010, 2018 annex 10.
19- WHO Technical Report Series, No. 929, Annex 5, 2005, Table A.1 (7) "A typical set of studies of the degradation paths of an active pharmaceutical ingredient".
20- Declaration of storage conditions for medicinal products particulars and active substances (Annex)
21- Quality Working Party questions and answers on API mix
22- ICH Q8 (R2) Pharmaceutical development - Scientific guideline
23- Process validation for finished products – information and data to be provided in regulatory submissions
24- Sterilization of the medicinal product, active substance, excipient and primary container
25- Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substances (FDA Guidance for Industry, 2018)
26- ICH Q3B (R2) Impurities in new drug products - Scientific guideline
27- Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action.
28- In-use stability testing of human medicinal products
29- Pharmaceutical quality of inhalation and nasal products - Scientific guideline
30- Quality of oral modified release products - Scientific guidelines.
31- Pharmaceutical development of intravenous medicinal products containing active substances solubilized in micellar systems (non-polymeric surfactants) - Scientific guideline
32- United States Pharmacopeia (USP)
33- European Pharmacopoeia (Eur.Ph)
34- British Pharmacopoeia (B.P)
35- Japanese Pharmacopoeia (J.P)
36- International Pharmacopeia.
37- Applicable EDA Guidance to be read in conjunction with this Guideline

-Quality Module Submission Guidance
-Soft File Arrangement Guidance

6. Annexes

NA