

**A REVIEW ON
COMPARATIVE STUDY OF DOSSIER FILES SUBMISSION PROCESS FOR
DRUG PRODUCT IN USA AND EUROPE**

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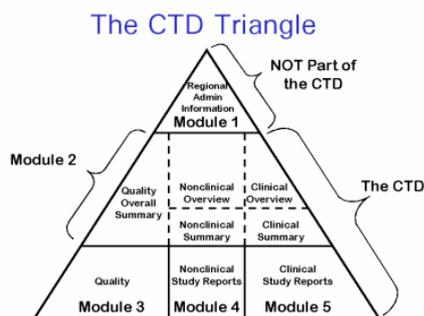
Summary

Dossier is a file document submitted based on the requirement of the approval of drug product. It is essential to submit dossier file in the form of common technical document in USA, Europe and Japan. Generic drugs are approved under ANDA submission in USA and in the form of MAA submission in Europe. CTD dossier divided in 5 modules such as Administrative and prescribing information, Overview and summary of modules 3 to 5, Quality Overall Summary (pharmaceutical documentation), Non clinical Document Safety (toxicology studies) and Clinical Document Efficacy (clinical studies). After compilation, dossier is submitted to regulatory authority. The regulations require three copies named as Archival (Blue), review (Red) and Field (Burgundy) copy in case of USA, and one copy (Binding color is not specified) for Europe.

Keywords: Dossier file, ANDA, Generic drugs, CTD, Regulatory authority

Introduction

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, U.S.) and the Ministry of Health, Labour and Welfare (Japan). The CTD is maintained by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).^{1,2}



The electronic Common Technical Document (eCTD) is an interface for the pharmaceutical industry to agency transfer of regulatory information. The content is based on the Common Technical Document (CTD) format.

It was developed by the International Conference on Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG). As of January 1, 2008, the U.S. Food and Drug Administration announced that the eCTD is the preferred format for electronic submissions.^{3,4,5}

¹⁸The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is a project that brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of pharmaceutical product registration.

The purpose of ICH is to reduce or obviate the need to duplicate the testing carried out during the research and development of new medicines by recommending ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration. Harmonisation would lead to a more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines while maintaining safeguards on quality, safety, and efficacy, and regulatory obligations to protect public health.¹⁸

⁷A generic drug (generic drugs, short: generics) is a drug which is produced and distributed without patent protection. The generic drug may still have a patent on the formulation but not on the active ingredient.

A generic must contain the same active ingredients as the original formulation. According to the U.S. Food and Drug Administration (FDA), generic drugs are identical or within an acceptable bioequivalent range to the brand name counterpart with respect to pharmacokinetic and pharmacodynamic properties. By extension, therefore, generics are considered (by the FDA) identical in dose, strength, route of administration, safety, efficacy, and intended use.⁷

ANDA (Generic) Drug Approval Process

An Abbreviated New Drug Application (ANDA) contains data which when submitted to FDA's Center for Drug Evaluation and Research, Office of Generic Drugs, provides for the review and ultimate approval of a generic drug product. Once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, low cost alternative to the American public.

A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics and intended use. All approved products, both innovator and generic, are listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book)*.

Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic applicants must scientifically demonstrate that their product is bioequivalent (i.e., performs in the same manner as the innovator drug). One way scientists demonstrate bioequivalence is to measure the time it takes the generic drug to reach the bloodstream in 24 to 36 healthy, volunteers. This gives them the rate of absorption, or bioavailability, of the generic drug, which they can then compare to that of the innovator drug. The generic version must deliver the same amount of active ingredients into a patient's bloodstream in the same amount of time as the innovator drug.

Using bioequivalence as the basis for approving generic copies of drug products was established by the "Drug Price Competition and Patent Term Restoration Act of 1984," also known as the Waxman-Hatch Act. This Act expedites the availability of less costly generic drugs by permitting FDA to approve applications to market generic versions of brand-name drugs without conducting costly and duplicative clinical trials. At the same time, the brand-name companies can apply for up to five additional years longer patent protection for the new medicines they developed to make up for time lost while their products were going through FDA's approval process. Brand-name drugs are subject to the same bioequivalence tests as generics upon reformulation.⁶

⁸The Common Technical Document is divided into five modules:

1. Administrative and prescribing information
2. Overview and summary of modules 3 to 5
3. Quality Overall Summary (pharmaceutical documentation)
4. Non clinical Document Safety (toxicology studies)
5. Clinical Document Efficacy (clinical studies)⁸

Module 1 - Administrative and Prescribing Information

Module 1 should contain all administrative documents (e.g., application forms, claims of categorical exclusion and certifications), and labeling, including the documents described below, as needed. Documents should be organized in the order listed below. Generally, all of the documents in Module 1 can be provided in a single volume. Environmental assessments should be submitted separately.⁹

1. FDA form 356h

The first document in Module 1 should be FDA form 356h.

2. Comprehensive table of contents

The next document in Module 1 should be the comprehensive table of contents for the entire submission. Each NDA and ANDA submission is required to have a comprehensive table of contents or index for the entire submission as described in 21 CFR 314.50 and 314.94. The comprehensive table of contents significantly enhances the usefulness of the document. It should include a complete list of all documents provided in the submission by module.

In the table of contents, you should identify the location of each document 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 (e.g., patent certification, financial disclosure) or section heading according to the CTD format (e.g., 3.2.P.4.2). If the full name of the document is too long for the tab identifiers, you should substitute an alternative name that adequately identifies the document. You should not use page numbers in the table of contents to refer to documents, but use tab identifiers as described above.

3. Administrative documents

a. Administrative document

You should provide the appropriate administrative documents with the submission. Examples of administrative documents are listed below. See 21 CFR 314.50, 314.94, and 601.2 for details on the administrative documents needed for specific submissions. FDA form 356h lists most of the administrative documents to be included in Module 1. The order of such documents should be consistent with that in FDA Form 356h.

- Patent information on any patent that claims the drug, if applicable
- Patent certifications (not for BLA)
- Debarment certification
- Field copy certification (not for BLA)
- User fee cover sheet
- Financial disclosure information
- Letters of authorization for reference to other applications or drug master files
- Waiver requests
- Environmental assessment or request for categorical exclusion
- Statements of claimed exclusivity and associated certifications

Since these documents are small, you should place them in the same volume, separated by tab identifiers. If you submit an environmental assessment, you should provide it as a separate volume.

b. Prescribing information

You should include all copies of the labels and all labeling for the product in Module 1. The type of labeling provided depends on the submission. Examples of prescribing information include container and package labels as well as package inserts, draft labeling, patient leaflets, information sheets, and required Medication Guides. You should separate each sample of labeling by tab identifiers.

c. Annotated labeling text

For the NDA, you should provide a copy of the proposed labeling text with annotations directing reviewers to the information in the summaries and other modules that support each statement in the labeling, as described in 21 CFR 314.50(c)(2)(i). The annotated labeling text should include the content of the labeling described under 21 CFR 201.57 and all text, tables, and figures used in the package insert.

d. Labeling comparison

For the ANDA, you should provide the comparison of labeling that is described in 21 CFR 314.94(a)(8).⁹

Module 2 - Common Technical Document Summaries

Module 2 should include the summary documents. You should provide the documents for this module in the order described below.

1. Overall CTD table of contents

For the first document in this module, you should provide a comprehensive table of contents listing all of the documents provided in the submission for modules 2 through 5.

2. Introduction to the summary documents

You should provide the introduction to the summary described in the guidance document M4: Organization of the CTD as a one page document.

3. Overviews and summaries

Module 2 should contain the following additional documents as described in the appropriate guidance documents (M4Q: The CTD -Quality, M4S: The CTD - Safety, M4E: The CTD - Efficacy):

- Quality overall summary (2.3, Module 2, section 3)
- Non clinical overview (2.4)
- Clinical overview (2.5)
- Nonclinical summary (2.6)
- Clinical summary (2.7)

The nonclinical summary and the clinical summary should be provided in separate volumes for ease of use by reviewers.^{9,10}

3.1 MODULE 3

TABLE OF CONTENTS

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

3.2 BODY OF DATA

3.2. S DRUG SUBSTANCE [NAME, MANUFACTURER]4

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 Nonproprietary Name (INN)
- Compendial name if relevant
- Chemical name(s)
- Company or laboratory code
- Other nonproprietary 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 [name, manufacturer]

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

3.2. S.1.3 General Properties [name, manufacturer]

A list should be provided of physicochemical and other relevant properties of the drug substance, including biological activity for Biotech.

General information regarding drug substance is given in ICH guidances Q6A and Q6B.

3.2. S.2 Manufacture [name, manufacturer]

3.2. S.2.1 Manufacturers [name, manufacturer]

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 [name, manufacturer]

The description of the drug substance manufacturing process represents the applicant's commitment for the manufacture of the drug substance. Information should be provided to adequately describe the manufacturing process and process controls. For example:

A flow diagram of the synthetic processes should be provided that includes molecular formulas, weights, yield ranges, chemical structures of starting materials, intermediates, reagents, and drug substance reflecting stereochemistry, and that 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, and time).

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.

Information demonstrating that materials (including biologically sourced materials (e.g., media components, monoclonal antibodies, enzymes)) meet standards appropriate for their intended use (including the clearance or control of adventitious agents) should be provided, as appropriate.

Information regarding drug substance's manufacturer is given in ICH guidances Q6A and Q6B.

3.2. S.2.4 Controls of Critical Steps and Intermediates [name, manufacturer]

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

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

Information regarding Controls of Critical Steps and Intermediates of drug substance are given in ICH guidances Q6A and Q6B.

3.2. S.2.5 Process Validation and/or Evaluation [name, manufacturer]

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

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 nonclinical, clinical, scale-up, pilot, and, if available, production scale batches.

Information regarding process validation and manufacturing process development is given in ICH guidance Q3A.

3.2. S.3 Characterization [name, manufacturer]

3.2. S.3.1 Elucidation of Structure and other Characteristics [name, manufacturer]

Confirmation of structure based on, for example, 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.

Information regarding characterization of drug substances is given in ICH guidance Q6A.

3.2. S.3.2 Impurities [name, manufacturer]

Information on impurities should be provided.

Information regarding impurities present in drug substance is given in ICH guidance Q3A, Q3C, Q5C, Q6A, and Q6B.

3.2. S.4 Control of Drug Substance [name, manufacturer]

3.2. S.4.1 Specification [name, manufacturer]

The specification for the drug substance should be provided.

Information regarding control of drug substance's specification is given in ICH guidances Q6A and Q6B.

3.2. S.4.2 Analytical Procedures [name, manufacturer]

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

Information regarding control of drug substance's analytical procedure is given in ICH guidances Q2A and Q6B.

3.2. S.4.3 Validation of Analytical Procedures [name, manufacturer]

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

Information regarding Validation of Analytical Procedures is given in ICH guidances Q2A, Q2B, and Q6B.

3.2. S.4.4 Batch Analyses [name, manufacturer]

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

Information regarding Batch Analyses is given in ICH guidances Q3A, Q3C, Q6A, and Q6B.

3.2. S.4.5 Justification of Specification [name, manufacturer]

Justification for the drug substance specification should be provided.

Information regarding justification of specification is given in ICH guidances Q3A, Q3C, Q6A, and Q6B.

3.2. S.5 Reference Standards or Materials [name, manufacturer]

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

Information regarding Reference standard is given in ICH guidances Q6A and Q6B.

3.2. S.6 Container Closure System [name, manufacturer]

A description of the container closure systems 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). Noncompendial methods (with validation) should be included, where appropriate.

For nonfunctional 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.

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 regarding storage conditions and retest date or shelf life, as appropriate.

Information regarding Container Closure System and Stability is given in ICH guidances Q1A, Q1B, and Q5C.

3.2. S.7.2 Postapproval Stability Protocol and Stability Commitment [name, manufacturer]

The postapproval stability protocol and stability commitment should be provided.

Information about Postapproval Stability Protocol and Stability Commitment is given in ICH guidances Q1A and Q5C.

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

Information about Stability Data is given in ICH guidances Q1A, Q1B, Q2A, Q2B, and Q5C.^{9,11,12,13}

3.2. P DRUG PRODUCT [NAME, DOSAGE FORM]

3.2. P.1 Description and Composition of the Drug Product [name dosage form]

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

Information about Description and Composition of the Drug Product is given in ICH guidances 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 application. The studies described in this section should be 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. Additional supportive data can be referenced to the relevant nonclinical or clinical sections of the application.

Information regarding Pharmaceutical Development is given in ICH guidances Q6A and Q6B.

3.2. P.2.1 Components of the Drug Product [name, dosage form]

3.2. P.2.1.1 Drug Substance [name, dosage form]

The compatibility of the drug substance with the excipients listed in 3.2.P.1 should be discussed.

Additionally, key physicochemical characteristics (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 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 listed in 3.2.P.1, their concentration, and the characteristics that can influence the drug product performance should be discussed relative to their respective functions.

3.2. P.2.2 Drug Product [name, dosage form]

3.2. P.2.2.1 Formulation Development [name, dosage form]

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

3.2. P.2.2.2 Overages [name, dosage form]

Any overages in the formulations described in P1 should be justified.

3.2. P.2.2.3 Physicochemical and Biological Properties [name, dosage form]

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 [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 in 3.2.P.3.3 that can influence the performance of the product should be discussed.

3.2. P.2.4 Container Closure System [name, dosage form]

The suitability of the container closure system (described in 3.2.P.7) for the storage, transportation (shipping), and use of the drug product should be discussed. This discussion should consider, for example, 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 [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 nonsterile 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 drug product with reconstitution diluents 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.

3.2. P.3 Manufacture [name, dosage form]

3.2. P.3.1 Manufacturers [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.

3.2. P.3.2 Batch Formula [name, dosage form]

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 [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 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 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).

All detail about Pharmaceutical Development, Manufacture is discussed in ICH guidance Q6B.

3.2. P.3.4 Controls of Critical Steps and Intermediates [name, dosage form]

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

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

Information of Controls of Critical Steps and Intermediates is given in ICH guidances Q2A, Q2B, 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).

Information of Process Validation and/or Evaluation is given in ICH guidance 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.

All about Control of Excipients's specifications is given in ICH guidances 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.

All about Analytical Procedures is given in ICH guidances Q2A and Q6B.

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.

All about Validation of Analytical Procedures is given in ICH guidances Q2A, Q2B, and Q6B.

3.2. P.4.4 Justification of Specifications [name, dosage form]

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

All about Justification of Specifications is mentioned in ICH guidances 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, viral safety data).

All about Excipients of Human or Animal Origin is given in ICH guidances Q5A, Q5D, and Q6B.

3.2. P.4.6 Novel Excipients [name, dosage form]

For excipients 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.

3.2. P. 5 Control of Drug Product [name, dosage form]

3.2. P.5.1 Specifications [name, dosage form]

The specifications for the drug product should be provided. Information about control of drug product's specifications is given in ICH guidances Q3B, Q6A, and Q6B.

3.2. P.5.2 Analytical Procedures [name, dosage form]

The analytical procedures used for testing the drug product should be provided. Information regarding analytical procedures is given in ICH guidances Q2A 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 drug product should be provided.

Information regarding validation of analytical procedures is given in ICH guidances Q2A, Q2B, and Q6B.

3.2. P.5.4 Batch Analyses [name, dosage form]

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

Information regarding batch analysis is given in ICH guidances Q3B, Q3C, Q6A, and Q6B.

3.2. P.5.5 Characterization of Impurities [name, dosage form]

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

Information regarding characterization of impurities is given in ICH guidances Q3B, Q5C, Q6A, and Q6B.

3.2. P.5.6 Justification of Specifications [name, dosage form]

Justification for the proposed drug product specifications should be provided. Information regarding justification of specification is given in ICH guidances 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 drug product should be provided if not previously provided in 3.2.S.5, Reference Standards or Materials.

Information regarding reference standards is given in ICH guidances Q6A and Q6B.

3.2. P.7 Container Closure System [name, dosage form]

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). Noncompendial methods (with validation) should be included where appropriate.

For nonfunctional 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.

3.2. P.8 Stability [name, dosage form]

3.2. P.8.1 Stability Summary and Conclusion [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 regarding storage conditions and shelf life, and, if applicable, in-use storage conditions and shelf life.

Information regarding Container Closure System and Stability is given in ICH guidances Q1A, Q1B, Q3B, Q5C, and Q6A.

3.2. P.8.2 Postapproval Stability Protocol and Stability Commitment [name, dosage form]

The postapproval stability protocol and stability commitment should be provided.

Information regarding Post approval Stability Protocol and Stability Commitment is given in ICH guidances 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, graphic, 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.

Information of stability data is given in ICH guidances Q1A , Q1B, Q2A, Q2B, and Q5C.^{9,14,15}

Module 4 - Nonclinical Study Reports

Module 4 should contain the nonclinical study reports and related information. You should provide the documents for this module in the order described below.

1. Module 4 table of contents

The first document in this module should be a table of contents listing all of the documents provided for module 4. See the guidance to industry M4S: The CTD - Safety for the headings and order to be used in the table of contents, including numbering of section headings.

2. Study reports and related information

You should provide each study report and each related document as an individual document, separated from the other documents by binders or tab identifiers. These documents should be presented in the order in which they are listed in the table of contents.

3. Literature References

Each literature reference should be provided as an individual document, separated from the others by tab dividers.⁹

MODULE 5: CLINICAL STUDY REPORTS

Reports of Biopharmaceutical Studies

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

Bioavailability (BA) Study Reports

This section should include the following BA studies.

- 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
- Food-effect studies

Comparative 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 can 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
- Similar drug products from different manufacturers

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 Section 5.3.1.3. Reports of in vitro dissolution tests used for batch quality control and/or batch release should be placed in the Quality Section of the CTD.

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.

Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

Human biomaterials is a term used to refer to proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess PK properties of drug substances. Examples include cultured human colonic cells that are used to assess permeability through biological membranes and transport processes and human albumin that is used to assess plasma protein binding. Of particular importance is the use of human biomaterials such as hepatocytes and/or hepatic microsomes to study metabolic pathways and to assess drug-drug interactions with these pathways. Studies using biomaterials to address other properties (e.g., sterility or pharmacodynamics) should not be placed in the Clinical Study Reports Section, but in the Nonclinical Study Section (Module 4).

Plasma Protein Binding Study Reports

Ex vivo protein binding study reports should be provided here. Protein binding data from PK blood and/or plasma studies should be provided in Section 5.3.3.

Reports of Hepatic Metabolism and Drug Interaction Studies

Reports of hepatic metabolism and metabolic drug interaction studies with hepatic tissue should be placed here.

Reports of Studies Using Other Human Biomaterials

Reports of studies with other biomaterials should be placed in this section.

Reports of Human Pharmacokinetic (PK) Studies

Assessment of the PK of a drug in healthy subjects and/or patients is considered critical to designing dosing strategies and titration steps, to anticipating the effects of concomitant drug use, and to interpreting observed pharmacodynamic differences. These assessments should provide a description of the body's handling of a drug over time, focusing on maximum plasma concentrations (peak exposure), area-under-curve (total exposure), clearance, and accumulation of the parent drug and its metabolites, in particular those that have pharmacological activity.

The PK studies whose reports should be included in Sections 5.3.3.1 and 5.3.3.2 are generally designed to (1) measure plasma drug and metabolite concentrations over time, (2) measure drug and metabolite concentrations in urine or feces when useful or critical, and/or (3) measure drug and metabolite binding to protein or red blood cells. On occasion, PK studies may include measurement of drug distribution into other body tissues, body organs, or fluids (e.g., synovial fluid or cerebrospinal fluid), and the results of these tissue distribution studies should be included in Section 5.3.3.1 or 5.3.3.2, as appropriate. These studies should characterize the drug's PK and provide information about the absorption, distribution, metabolism, and excretion of the drug and any active metabolites in healthy subjects and/or patients. Studies of mass balance and changes in PK related to dose (e.g., determination of dose proportionality) or time (e.g., due to enzyme induction or formation of antibodies) are of particular interest and should be

included in Sections 5.3.3.1 and/or 5.3.3.2. Apart from describing mean PK in normal and patient volunteers, PK studies should also describe the range of individual variability. In the ICH guidance on ethnic factors in the acceptance of foreign data (ICH E5), factors that may result in different responses to a drug in different populations are categorized as *intrinsic ethnic factors* or *extrinsic ethnic factors*. In this M4E guidance, these categories are referred to as *intrinsic factors* and *extrinsic factors*, respectively. Additional studies can also assess differences in systemic exposure as a result of changes in PK due to intrinsic (e.g., age, gender, racial, weight, height, disease, genetic polymorphism, and organ dysfunction) and extrinsic (e.g., drug-drug interactions, diet, smoking, and alcohol use) factors. Reports of PK studies examining the influence of intrinsic and extrinsic factors on exposure should be organized in Sections 5.3.3.3 and 5.3.3.4, respectively.

In addition to standard multiple-sample PK studies, population PK analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose-PK-response relationship. Because the methods used in population PK studies are substantially different from those used in standard PK studies, population PK studies should be placed in Section 5.3.3.5.

Healthy Subject PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in healthy subjects should be placed in this section.

Patient PK and Initial Tolerability Study Reports

Reports of PK and initial tolerability studies in patients should be placed in this section.

Intrinsic Factor PK Study Reports

Reports of PK studies to assess effects of intrinsic factors should be placed in this section.

Extrinsic Factor PK Study Reports

Reports of PK studies to assess effects of extrinsic factors should be placed in this section.

Population PK Study Reports

Reports of population PK studies based on sparse samples obtained in clinical trials including efficacy and safety trials should be placed in this section.

Reports of Human Pharmacodynamic (PD) Studies

Reports of studies with a primary objective of determining the PD effects of a drug product in humans should be placed in this section. Reports of studies whose primary objective is to establish efficacy or to accumulate safety data should be placed in Section 5.3.5.

This section should include reports of (1) studies of pharmacologic properties known or thought to be related to the desired clinical effects (biomarkers), (2) short-term studies of the main clinical effect, and (3) PD studies of other properties not related to the desired clinical effect. Because a quantitative relationship of these pharmacological effects to dose and/or plasma drug and metabolite concentrations is usually of interest, PD information is frequently collected in dose-response studies or together with drug concentration information in PK studies (concentration-response or PK/PD studies). Relationships between PK and PD effects that are not obtained in well-controlled studies are often evaluated using an appropriate model and used as a basis for designing further dose-response studies or, in some cases, for interpreting effects of concentration differences in population subsets.

Dose-finding, PD, and/or PK-PD studies can be conducted in healthy subjects and/or patients and can also be incorporated into the studies that evaluate safety and efficacy in a clinical indication. Reports of dose-finding, PD, and/or PK/PD studies conducted in healthy subjects should be placed in Section 5.3.4.1, and the reports for those studies conducted in patients should be placed in Section 5.3.4.2.

In some cases, the short-term PD, dose-finding, and/or PK-PD information found in pharmacodynamic studies conducted in patients will provide data that contribute to assessment of efficacy because they show an effect on either an acceptable surrogate marker (e.g., blood pressure) or a clinical benefit endpoint (e.g., pain relief). Similarly, a PD study can contain important clinical safety information. When these studies are part of the efficacy or safety demonstration, they are considered clinical efficacy and safety studies that should be included in Section 5.3.5, not in Section 5.3.4.

Healthy Subject PD and PK/PD Study Reports

PD and/or PK/PD studies having nontherapeutic objectives in healthy subjects should be placed in this section.

Patient PD and PK/PD Study Reports

PD and/or PK/PD studies in patients should be submitted in this section.

Reports of Efficacy and Safety Studies

This section should include reports of all clinical studies of efficacy and/or safety carried out with the drug, conducted by the sponsor or otherwise available, including all completed and all ongoing studies of the drug in proposed and nonproposed indications. The study reports should provide the level of detail appropriate to the study and its role in the application. ICH E3 describes the contents of a full report for a study contributing evidence pertinent to both safety and efficacy. Abbreviated reports can be provided for some studies (see ICH E3 and individual guidance by region).

Within Section 5.3.5, studies should be organized by design (controlled, uncontrolled) and, within controlled studies, by type of control. Within each section, studies should be categorized further, ordered by whether the study report is complete or abbreviated (ICH E3), with completely reported studies presented first. Published reports with limited or no further data available to the sponsor should be placed last in this section.

In cases where the application includes multiple therapeutic indications, the reports should be organized in a separate Section 5.3.5 for each indication. In such cases, if a clinical efficacy study is relevant to only one of the indications included in the application, the study should be included in the appropriate Section 5.3.5; if a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate Section 5 and referenced as appropriate in other Sections 5.3.5 (e.g., Section 5.3.5A, Section 5.3.5B)

Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

The controlled clinical study reports should be sequenced by type of control:

- Placebo control (could include other control groups, such as an active comparator or other doses)
- No-treatment control
- Dose-response (without placebo)
- Active control (without placebo)

- External (historical) control, regardless of the control treatment

Within each control type, where relevant to assessment of drug effect, studies should be organized by treatment duration. Studies of indications other than the one proposed in the application, but that provide support for efficacy in the proposed use, should be included in Section 5.3.5.1.

Where a pharmacodynamic study contributes to evidence of efficacy, it should be included in Section 5.3.5.1. The sequence in which studies were conducted is not considered pertinent to their presentation. Thus, placebo-controlled trials, whether early or late, should be placed in Section 5.3.5.1. Controlled safety studies, including studies in conditions that are not the subject of the application, should also be reported in Section 5.3.5.1.

Study Reports of Uncontrolled Clinical Studies

Study reports of uncontrolled clinical studies (e.g., reports of open label safety studies) should be included in Section 5.3.5.2. This includes studies in conditions that are not the subject of the marketing application.

Reports of Analyses of Data from More than One Study (Including Any Formal Integrated Analyses, Meta-Analyses, and Bridging Analyses)

Many clinical issues in an application can be addressed by an analysis considering data from more than one study. The results of such an analysis should generally be summarized in the clinical summary documents, but a detailed description and presentation of the results of such analyses are considered critical to their interpretation. Where the details of the analysis are too extensive to be reported in a summary document, they should be presented in a separate report. Such reports should be placed in Section 5.3.5.3. Examples of reports that would be placed in this section include (1) a report of a formal meta-analysis or extensive exploratory analysis of efficacy to determine an overall estimate of effect size in all patients and/or in specific subpopulations and (2) a report of an integrated analysis of safety that assesses such factors as the adequacy of the safety database, estimates of event rates, and safety with respect to variables such as dose, demographics, and concomitant medications. A report of a detailed analysis of bridging, considering formal bridging studies, other relevant clinical studies, and other appropriate information (e.g., PK and PD information), should be placed in this section if the analysis is too lengthy for inclusion in the Clinical Summary.¹⁶

General Issues for Submissions

Regulations in 21 CFR 314.50, 314.94, and 601.2 provide general requirements for submitting NDAs, ANDAs, and BLAs, respectively. This section addresses briefly some general issues related to providing marketing applications in paper format.

A. Amendments and Supplements

Although the CTD describes the agreed to common format for the preparation of the original application, you can use it for supplements to an original application or amendments to either the original application or subsequent supplements. General correspondence should be included in Module 1.

You can use the CTD format for submissions whether or not the previous submission was in the CTD format. You should not mix the CTD and older formats in the same module. We will consider, on a case-by-case basis, accepting submissions where some modules

are provided in the CTD format and the rest of the submission is not in the CTD format. You should discuss this possibility at the pre NDA/BLA meeting or earlier.

B. Organizing Documents

You should bind all documents in separate volumes, or documents can be combined in volumes as long as they are separated by appropriately named tab identifiers. For example, the user fee cover sheet for a submission should be separated from the other documents by a tab identifier named user fee cover sheet. In general, documents from different CTD modules should not be included in the same volume. You may want to combine documents from different modules in the same volume for amendments consisting of a small number of short documents.

C. Number of copies

The regulations require archival, review, and field copies of NDAs and ANDAs. For BLAs, archival and review copies are generally submitted. The archival copy includes the entire submission. The review and field copies require only a portion of the application.

1. Archival copy

The archival copy is a complete copy of the application. It serves as the official archive of the application and may be used during the review of the application.

2. Review copy

Review copies are in addition to the archival copy and include the information needed by each review discipline for its evaluation. These copies facilitate the concurrent review of the application by the different review disciplines. Review copies that may be necessary according to 21 CFR 314.50 for an individual submission include:

- Quality (Module 3),
- Nonclinical (Module 4),
- Clinical (Module 5) - safety and efficacy documents for clinical reviewer
- Clinical (Module 5) - safety and efficacy documents for the statistical reviewer,
- Clinical (Module 5) - clinical pharmacology and pharmacokinetics documents (or bioequivalence documents for ANDAs), and
- Clinical (Module 5) - clinical microbiology documents.

You should include a copy of Modules 1 and 2 in each review copy. Each review copy should be labeled and bound separately.

It is recommended that you contact the office with the responsibility for the review of your product to determine how many copies of each module or sections of modules should be submitted.

3. Field copy

The field copy should be a separately bound copy of the Quality section (Module 3) for the NDA and ANDA. You should send this copy directly to the appropriate field office. A field copy is not required for the BLA.

D. Paper size

You should use standard U.S. letter size paper (8.5 x 11 inches) for all submissions. Occasionally, you may want to use individual pages larger than standard paper size to present a floor plan, synthesis diagram, batch formula, or manufacturing instructions. These pages should be folded and mounted so they may be opened for review without disassembling the jacket and refolded without damage when the volume is shelved.

E. Paper margins

We have found that a margin of at least 0.75 inches from the bound edge of the printed page prevents information from being obscured when the paper is placed in a binder. Other margins can be as small as 0.25 inches from the edge of the page. You can submit documents printed on both sides of a page, provided legibility is not impaired and margin space is sufficient on both the left and right side, so that information is not obscured when the page is placed in a binder.

F. Fonts

Font size for text and tables should be of a style and size that is large enough to be easily legible, even after photocopying or when provided electronically. We recommend that narrative text be submitted in Times New Roman 12 point font. Generally, font sizes 9 to 10 points are considered acceptable in tables, but you should avoid fonts smaller than 12 points whenever possible. When choosing a font size for tables, it is important to balance the desirability of providing sufficient information on a single page to facilitate data comparisons with that of maintaining a font size that remains readable. If the font size is too large, data comparisons may be complicated because data may be presented in multiple tables. Ten point font is recommended for footnotes.

G. Binding volumes

All pages should be submitted with three holes punched on the left side of the page and bound with fasteners, rather than placed in ring binders.

We recommend using polyvinyl type binders (0.23 to 0.25 gauge) for the archival copies and extra heavy paper binders for the review and field copies. A limited number of binders can be obtained by calling the number below. The quantity that can be ordered at any one time is determined by the U.S. Government Printing Office (GPO). U. S.

Government Printing Office
Washington, D.C. 20404-0001
(202) 512-1800
Program #B511-S

Additional binders can be purchased from commercial sources.

The front cover of the binder should be 9 by 11.5 inches, and the back cover should be 9 by 12 inches. You should use colored binders to distinguish the different copies of the applications. The archival copy should be blue. For ANDAs, the review copy should be red. For ANDAs and NDAs, the field copy should be green. The color for the NDA or BLA review copy binders depends on the type of information in the copy. See Table 2 for details.

Table 2: Binder Colors for NDA and BLA Review Copies

Review copy for:	Binder color
Quality	Red
Nonclinical	Yellow
Clinical- pharmacokinetics and bioavailability	Orange
Clinical - microbiology	White
Clinical - safety and efficacy - clinical	Tan
Clinical - safety and efficacy - statistical	Green

H. Volume size

Volumes should not be more than 2 inches thick. Volumes thicker than 2 inches are difficult for both the document room personnel and reviewers to handle.

I. Volume numbering

You should number the volumes by module, resulting in a separate set of numbers for each module.

J. Volume identification

You should print the following information prominently in the central portion of the front cover of each volume:

- Name of applicant
- Name of product
- Application number, if available
- Module number and name

On the front, lower right hand corner of each binder, you should print the volume number in the following format: x of y volumes where x is the number for the specific volume and y is the total number of volumes submitted for the respective module. For example, volume 6 for the Safety module with a total of 50 volumes for the module would have 6 of 50 volumes in the lower right hand corner. The volumes in the module copy should be numbered sequentially.

On the front, upper right hand corner, you should print "Module __ Volume ____". You should fill in this blank for the initial submission of the application using the format Module m Volume s.x, where m is the module number, s is the sequence number of the submission and x is the number of the specific volume in each module. For example, if the first submission for an application is a chemistry presubmission, volume 15 of the presubmission would be named Module 3, Volume 1.15.

All copies of the submission, including the review copies, should use the same volume numbers. However, the volume numbers may not be consecutive in the review copy since the review copy may only include a portion of the information in the archival copy.

K. Pagination

Page numbering should be at the document level and not at the volume or module level. (The entire submission should never be numbered consecutively by page.) In general, all documents should have page numbers. Since the page numbering is at the document level, there should only be one set of page numbers for each document.

If you include a document within a document, such as a protocol within a study report, the document to be included (in this case, the protocol) should be attached as an appendix. You should demarcate each appendix with an appropriately named tab identifier. For example, if the protocol is the first appendix, the tab should be named *Appendix A* or *Protocol* or some equivalent.

L. Cross referencing documents

You should reference documents by volume, CTD module, tab identifier, and page number.

M. Packing carton

To help us in storing submission volumes, we ask that you ship the volumes in boxes measuring 14 x 12 x 9.5 inches. On the outside of the carton, you should include the following information:

- Applicant's name
- Drug/biologic name
- Volume numbers included in the box
- Boxes should be numbered 1 of n, 2 of n, 3 of n, and so on.
- Type of copy included in the box (e.g., archival, clinical, safety, and efficacy review copy)

N. Sending the Submission*1. CBER*

Send all submissions to the Document Control Center (DCC). The address for the DCC can be found at the CBER web site at www.fda.gov/cber.

2. CDER

For the NDA, you should send the initial paper submission to the central document room. You should send all other submissions to the appropriate division document room for NDAs or, for ANDAs, to the Office of Generic Drugs. The addresses for the document rooms can be found at the CDER web site at www.fda.gov/cder. All submissions with electronic components should be sent to the central document room.¹⁷

Comparison Table of Regulatory Requirement between USA and Europe
Administrative

Requirement	USA	EU
Application	ANDA	MAA
Approval Time line	18 Month	12 Month
Copies	3 (archival, review, field)	1
Debardment certification	Required	Not required
Pharmacovigilance	Not required	Required
Agent Authorization	Required	Not required

Manufacturing and control

Requirement	USA	EU
No. of batches	1	3
Packaging	Minimum 1 lakh units	Not required
Process validation	Not required at the time of submission	Required if it is MR formulation or aseptic product

Finish Product control

Requirement	USA	EU
Assay	90-100%	95-105%
Identification Test	Single test	Additional test required
Color identification	Not required	Required
Water content	Required	Not Required
Disintegration test	Not required	Required

Labeling requirement

Requirement	USA	EU
NDC No.	Required (10 digit)	Not required
Prescription status	R _x	POM
Labels	Vials/ Carton/ PIL	Vials/ Carton/ PIL/ SPC
Side by side comparison	Vials/ Carton/ PIL	Not required
Readability testing	Not required	Required

Stability requirement

Requirement	USA	EU
No. of batches	1	2
Date and time of submission	3 Month accelerated and 3 month long term	6 month accelerated and 6 month long term
Container orientation	Inverted and upright	Do not addressed

Bioequivalence requirement

Requirement	USA	EU
CRO	Audited by FDA	Audited by MHRA
Reserve Sample	5 times the sample required for analysis	No such requirement
Fasted/ Fed	As OGD recommendation	No such requirement
Retention of samples	5 years from the date of filling the application	No such requirement but usually followed
Biowaiver criteria	Wt. Proportionate/ Wt. similar/ SUPAC level III	Wt. Proportionate/ Wt. similar

Conclusion

From the above discussion we have conclude that CTD dossier provide a harmonized format, that will be acceptable in all three regions. Guidance indicates an appropriate format for the data that have been acquired but not what studies are required. Applicants should not modify individual formats. Information should be unambiguous and transparent to facilitate the review and help a reviewer to become quickly orientated. Text and tables should be prepared using margins that allow the document to be printed on A4 paper (EU and Japan) and 8.5x11" paper (USA) Times New Roman, 12-point font is recommended for narrative text.

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