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Review Article

# COMPARISON OF REGULATORY REQUIREMENTS FOR GENERIC DRUGS DOSSIER IN UNITED STATES AND EUROPE

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***ABSTRACT***

*Common technical document (CTD) provides a standardized structure for regulatory submissions that is acceptable in all ICH countries. Although the CTD makes multinational filing easier, there are significant differences in the dossier submission requirements in these countries. This study put forth the differences in registration requirements for generics in United States. Generic drug in US they are approved under the abbreviated new drug application. Bio availability and bio equivalence study data is critical in the generic drugs approval process. decentralized body which is responsible for safety regulation of the food and drug products in Europe, and the manufactured is obligated to establish bioequivalence of their drug to the 'European reference product'.*

***KEYWORDS:*** *CTD, generic drugs, bioequivalence, MAA.*

## INTRODUCTION

**Definition:**

A generic drug (generic drugs, short: generics) is a drug defined as" a drug product that is comparable to a brand/reference listed drug product in dosage form, strength, quality and Performance characteristics, and intended use".

A generic drug 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 pharmacodynamics properties. By extension, therefore, generics are considered (by the FDA) identical in dose, strength, route of administration, safety, efficacy, and intended use [1].

**Overview of ICH:**

The ICH was founded in April 1990 at a meeting of the European Federation of pharmaceutical Industries Association (EFPIA) in Brussels. ICH is a unique undertaking that brings together the drug regulatory authorities and the pharmaceutical industry of Europe, Japan and the United States [2].

**ICH Objectives:**

- To prevent duplication of clinical in humans:
- To minimize the use of animal testing without compromising safety and effectiveness;
- To streamline the regulatory assessment process for new drug applications; and
- To reduce the development time and resources for drug development. Preparing and Organizing the CTD

In CTD, the display of information should be unambiguous and transparent, so as to facilitate the review of the basic data and to help a reviewer become quickly oriented to the application contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper and 8.5x11 paper (US). A margin of at least 0.75 inches from the bound edge of the printed page is required to prevent information from being obscured and to place the paper the paper in a binder. Narrative text is submitted in Times New Roman 12 point font. Generally, font sizes 9 to 10 points are considered acceptable in tables. Ten point's fonts are recommended for footnotes. Acronyms and abbreviations should be defined the first time they are used in each module. The CTD is divided into five modules.

Module 1-Administrative and prescribing information
Module 2-Overview and summary of modules 3 to 5
Module 3- Quality (pharmaceutical documentation)
Module 4-Non clinical document safety (toxicology studies)
Module 5-Clinical document efficacy (Clinical studies)

**2. Introduction of CTD:**

CTD is common technical documents which is a major project of the ICH to avoid the duplication and translation into regional language work of a single application. Through this, an applicant can file one single application to more than one country at a time for the registration of their drug product. According to ICH, all the technical requirements for the

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application of drug approval were harmonized in CTD format which are scientifically more elaborate by USFDA in quality Overall summary(QOS) and Overall efficacy(includes clinical overview and clinical summary).This way presentation of the registration documents has increased the efficiency in the FDA review process.

**The main Areas of Harmonization for CTD are:**

- Safety pharmacology
- Clinical pathology
- Immunotoxicology
- Juvenile toxicology studies
- Statistical methods in certain studies like mutagenicity, carcinogenicity and toxicokinetic studies during
- The 1st phase of ICH. So far, this has not been discussed in any ICH EWG and could be considered as a future topic.
- Recommendations for additional/ alternative methods of testing carcinogenicity.

The Common Technical Document is organized into five modules. The contents of Module 1 are different according to the competent authorities of the United States (FDA), the European Agency for the Evaluation of Medicinal products (EU). The modules are present in the triangular format which all the modules are the part of CTD except module 1 which is not the part of CTD and is different for different country. The different modules are as follows: [3]

***Module 1:*** It is related to submit regional and administrative information to the national regulatory agencies in which an applicant desires to file a market approval application as per their regulatory guidelines. Prescribing information (Such as labeling and packing inserts) also come under this module. It is totally different for different country.

***Module 2:*** It consists of the overviews and overall summaries related to the chemistry, manufacture, control (CMC), non-clinical, and clinical studies results conducted to prove the quality~ safety and efficacy of the drug product. This module includes the summaries of module 3, 4, and 5.

***Module 3:*** Quality-- It covers the complete pharmaceutical and technical aspects which can affect the quality of the drug product. From the formulation and development department (pharmaceutical development report) to the manufacturing (GMP) analysis and testing (GLP), packing, storage conditions, stability studies of the product.

***Module 4:*** Non-clinical study reports- it covers the complete Pharmacological, Toxicological study reports and information equivalent to the quality of the drug to provide the evidence of the safety of the drug product.

***Module 5:*** Clinical study Reports- The clinical trials and their reports carried out the human beings to list the desired effect of the drug product are included in this section. It is to provide to the regulatory authority containing the information which prove the efficacy of the drug. For generic drugs, the applicant only has to prove the bioavailability similar to that of innovator or branded innovator or branded drug only. To conduct such bioequivalence studies (BA-BE), healthy volunteers arc selected and to be conducted in a controlled manner.

Before CTD/eCTD application for the submission of a drug application, the procedure was different as per the country wise. In US, NDA, ANDA, BLA, Integrated summary of safety (ISS), integrated summary of Efficacy (ISE) was submitted for the approval of the product as show in the figure, so many duplicate copies were required to make according to the FDA [4].

**3. Registration of Drugs in United States:** [5-10]

**Regulatory Bodies:**

***1. The united states of food and drug administration (usfda):***

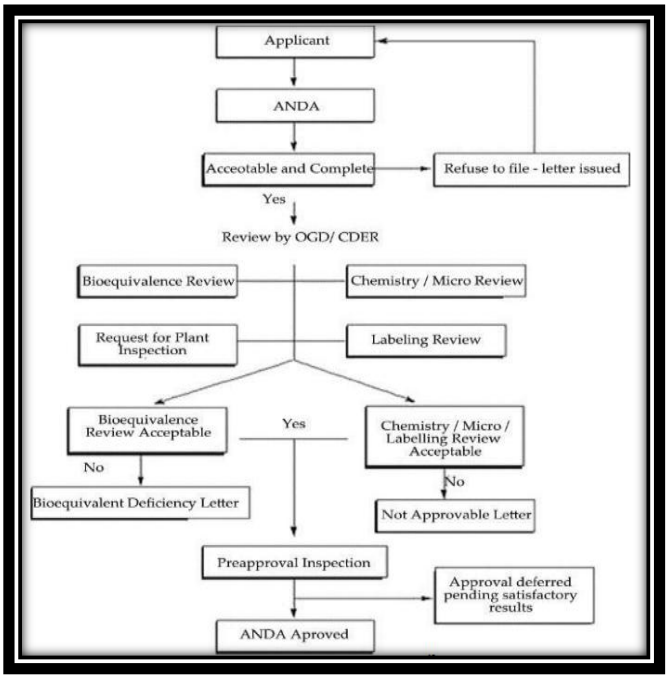
The FDA's Office of Generic Drugs (OGD) within the Canter for Drug Evaluation in Research ensures that people have access to safe, affordable generic drugs.

***Generic Drug Dossier Submission in US:*** [4]

Generic drugs are approved under ANDA (Abbreviated New Drug Application) in USA. New drugs, like other new products, are developed under patent protection. The patent protects the investment in the drug's development by giving the company the sole right to sell the drug while the patent is in effect. When patents or their periods of exclusivity expire, manufacturers can apply to the FDA to sell generic versions. The ANDA process does not require the drug sponsor to repeat costly animal and clinical research on ingredients or dosage forms already approved for safety and effectiveness.

In order to file ANDA all required items should be in proper order (organization). Detail information is available under Regulation 21 CFR 314.50, 21 CFR 314.94 and 21 CFR 314.440.

Office of Generic Drug (OGD) strongly encourages submission of the bioequivalence, chemistry and labeling portions an application in electronic format.




FDA has issued several guidance documents specific to the CTD and eCTD submissions. The information contained in these guidance focuses on the technical aspects of filling a CTD application and should be reviewed thoroughly prior to submitting an ANDA. This guidance addresses the content of the CTD for an original ANDA.

The CTD is comprised of the following modules:

*Module 1*: Administrative information;
*Module 2:* CTD Summaries;

*Module 3:* Quality;
*Module 4:* Nonclinical study reports; and
*Module 5:* Clinical Study reports.

The sections that follow in this guidance detail the information to be submitted in the applicable Modules, sections, and subsections.

***Module 1 - Administrative Information:***

- That the patent information has not been submitted to FDA (Paragraph l Certification)
- That the patent information has expired (Paragraph II certification)
- The date on which the patent will expire (Paragraph III certification)
- That the patent is invalid, unenforceable or will not be infringed by the manufacture use, or sale of the drug product for which the ANDA is submitted (Paragraph IV certification)
- Applicants submitting a Paragraph IV certification I (name of applicant, certify that patent No.------ (is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of) (name of proposed drug product) for which this application is submitted.

***Module 2- CTD Summaries:***

***1. Quality Overall Summary:*** 2.3 Contains the Quality Overall Summary (QOS), which provides overview of the chemistry, manufacturing, and controls (CMC) section of the application. The QOS summarizes what is known about the Drug substance (the active pharmaceutical ingredient (API) in sect ion 2.3.S drug product in section 2.3.P.

AU information provided in the summary needs to be accurate and supported by information, data, or justification included in Module 3 or other parts of the application.

The QOS

- Should not exceed 40 pages of test, excluding tables and figures.
- Introduction should not exceed one page.
- Should not exceed 80 pages for biotech and products manufactured using more complex process.

***Module 3 Quality:***

- Module 3 contains all of the CMC Information necessary to support the application, including the information supporting and verifying what was summarized in Module 2.3
- It is recommended that applicants review the following guidance 's for industry to assist in the preparation of Module 3: ANDAs: Impurities drug products (Ref. 16), ANDAs: Impurities Ref. in drug substance (Ref.17), and ANDAs: Stability Testing of Drug Substances and products.

***Module 4- Nonclinical Study Reports:***

- ANDA's generally do not contain data that are required for Module 4.

***Module 5 Clinical Study Reports:***

- Module 5 contains all of the clinical study report data needed to support the application and demonstrate that the generic is bioequivalent to the RLD. To facilitate the submission of complete data, FDA develops product specific guidance, summary data tables and multiple guidance on bio pharmaceutics. Applicants should use an eCTD study tagging file for each study submitted.

**4. Registration of Drugs in Europe:** [5-10]

***Regulatory Bodies:*** In Europe, the drugs are marketed only after the marketing authorization approval. European generic medicines are approved through 4 marketing authorisation procedures namely,

1. Centralized procedure.
2. Mutual-recognition procedure.
3. National procedure.
4. Decentralized procedure.

**Generic drugs in Europe:**

The European Medicines Agency (EMA) assesses applications from companies to market generic medicines in the European Union (EU). A generic medicine is developed to be the same as a medicine that has already been authorized, called the reference medicine.

The generic medicines industry is at the heart of public health delivery. This industry provides essential medicines that European patients, healthcare professionals and healthcare systems rely on to treat most acute and chronic ailments ranging from cardiovascular, to diabetes and even to cancer.

**Modules submission data for EUROPE**

**NeeS as per EMA:**

***Dossier Structure:*** Typically, a NeeS application should cover all dosage forms and strengths of a product with any one invented name.

In MRP/DCP, a single NeeS application should preferably be used for each procedure. If applicants decide to have one NeeS dossier per strength or form, they should inform the agencies in the cover letter.

Once a structure has decided and submitted for a product (strengths or forms), applicants should continue to use this structure for all subsequent NeeS dossier for the same product or communicate to authorities if a change is needed.

**MODULE-1:**

***Administrative Information:***

This module contains administrative information that is unique for each region. The name of the folder for module 1should be m1.

***1. General considerations:*** In the case of country specific files or folders the country code should appear in the file and folder name as the differentiating marking.

***2. Creation and Management Envelope Information:*** The CTD envelope should be used to describe the eCTD sequence

***3. Cover letter:*** The cover letter should always be submitted with the document operation attribute "new".

***4. Tracking Table:*** A tracking table should always be included as an annex to the cover letter for MRP and DCP. This is also highly recommended for CP and NP. The file should be named a CC-tracking pdf (e.g. ema tracking-var.pdf for the CP, common-tracking –var.pdf in an MRP/DCP, or be-tracking-var.pdf in a NP.)

***5. Application Forms:*** The application form should always be submitted with the document operation attributes "new", unless the error has been made in the form and an updated application form is been provided, in which case the operation attributes should be "replace".

Documents which do not fit into the M2-5 sections or response to questions (e.g. justification for changes, additional administrative information) should be placed as single documents after the application form.

***6. Product information:*** Product information should be supplied as pdf files but some NCAs and the EMA require an RTF or word file in addition to facilitate assessment. Those additional files should be provided in the separate folder working documents on the same CD/DVD.

***7. Use of Response Document Section:*** The submission of electronic information in response to a list of questions from NCAs and EMA should follow a same basic principles as the first submission. The written response should be submitted following the EU recommended response folder and file structure.

***8. Use of the additional Data section:*** The section additional data should only be used for nationally required information in national, Mutual recognition and Decentralized Procedures.

**MODULE-II:**

***Overviews and summaries:***

***General considerations:*** Each document should be provided as an individual PDF. The name of the folder for module 2 should be m2.

The folders in module 2 should be named as follows but can be further reduced or omitted to minimize path length issues.

**MODULE-III:**

***Quality:***

***1. Module 32S drug substance:*** If the product contains multiple drug substances, then documentation for each substance should be provided in its own m23s section. If a drug substance is manufactured at multiple different manufacturing companies, documentation can be provided in multiple m32s sections.

***2. Module 32P drug product:*** Each dosage form covered by eCTD application should be described in its own m32p section. If an application describes multiple strengths of any one dosage form, then documentation that covers all strengths can be provided in a single m32p section.

**MODULE-IV:**

***Nonclinical Study Reports:***

The name of the folder module 4 should be m4.

***Guidance on the handling of Granular study reports:*** Submission created in eCTD format for the use within the FDA may provide more granular study reports using study tagging files. There is no need to reorganize the report for submission to the EMA or NCAs.

**MODULE-V:**

***Clinical Study Reports:***

The name of the folder module 5 should be m5.

***1. Management and handling of Multiple Indications:*** If a clinical efficacy study is relevant to multiple indications, the study report should be included in the most appropriate subsection of m535 and reference as necessary in the equivalent section under the different indication.

***2. Management and Handling of Granular Clinical Study Reports:*** In order to maintain a consistent looking eCTD lifecycle and tablet of contents, applicants are advised to use node extensions for all clinical study reports, regardless of the granularity of the content.

ICH Q&A 22 recommends use of E3 granularity for clinical study reports. In Europe, node extensions should be used to group together individual files.

***3. Provisions of CRFs and Data when Requested:*** If case report. Forms and individual patient data listings are submitted in m537 they should place in the same order as the clinical study reports appearing in m535 and should be indexed by study. Please note the bookmarks will not be required as there will be no further internal structure.

***4. Provision of Synopses of Individual Studies:*** It is acceptable or either to include copies of the synopses for each study or to provide hyperlinks to synopses located in module 5 without providing copies. In either case listening of clinical studies should be provided and this should include hyperlinks to the first page of each synopsis.

***5. Company Core Data Sheet:*** If company submits their company core Data Sheet, this is recommended to be provided in post marketing experience.

**Table No. 1: Compassion of generic drug dossier submission in US and EUROPE**

| Requirements | United states | Europe |
|---|---|---|
| **Agency** | One Agency USFDA | ➢ Multiple Agencies<br>• EMEA<br>• CHMP<br>• National Health Agencies |
| **Registration process** | One registration process | ➢ Multiple Registration Process<br>• Centralized -(European Community)<br>• Decentralized - (At least 2 member states)<br>• Mutual Recognition -(At least 2 member states)<br>• National - (1 member state) |
| **Application** | ANDA | MAA |

| | | |
|---|---|---|
| **Stability Data** | The stability data for accelerated studies are submitted for three month at the time of original submission | The stability data for accelerated studies are submitted for six month at the time of original submission |
| **Approval time** | 18 months | 12 months |
| **Pharmacopeia's** | US Pharmacopeia | European Pharmacopoeia (Ph. Eur.) |
| **Batch size** | Minimum of 1,00,000 Units | Minimum of 1,00,000 Units |
| **Process validation** | Not required at the time of submission | Required at the time of submission |
| **Post-approval changes** | The changes in the approved drug can be done by filing PAS<br>CBE - 30 / CBE<br>Annual Report | ➢ The changes in the approved drug can be done by filing<br>• Type IA Variation<br>• Type IB Variation<br>• Type II Variation |

**Table No. 2: Comparison based on Modules in US and Europe**

| **Module 1:- Comparison based on Modules in US And Europe** | |
|---|---|
| **United states** | **Europe** |
| i. Administrative information is different i.e. cover letter, forms (356h), application information, field copy certification, debarment certification, financial certification, Patent information and exclusivity 18. | i. Administrative information such as cover letter specified for the particular country, application form applicable in that country, exclusivity statement, proof of payment to clinical investigators, proof of establishment of the applicant in EEA. |
| ii. The paper size for the submission is Letter size (8.5x11 inches) with font Size 12 in times new roman format. The tables and figures have small font size i.e. 8 to 10. | ii. A4 (8.27x11.69inches) paper size is used for the dossier preparation with font size 12 in times new roman format. |
| iii. Package inserts are provided for drug product in labeling. | iii. SPC (summary of product characteristic) is provided about the drug product in libeling. |
| iv. Proposed Labels and cartons with proper dimensions similar to that of the RLD labels are provided. | iv. Mock ups and specimens of labels and cartons sent with the application as appropriate. Braille is used for the libeling conditions on the labels. |
| v. Request for waiver of in-vivo BE studies is provided in the module 1. | v. Request for waiver is not provided in the module 1. |
| vi. Annotated draft labeling (side by side) for labels and cartons compared with the RLD with proper annotation is provided. | vi. No annotation (side by side) for libeling is provided. Everything is provided in the SPC and package inserts. |
| vii. The EAS (Environment Assessment Statement) for categorical exclusion certification in compliance with the law of EPA of US is provided. | vii. Environ risk Certification21 is given with the information for GMO or Non - GMO. The fresh/new certificate is provided. |
| viii. Risk management Plans section is for the post marketing surveillance and controlling the adverse effects of the drugs by proper management. This is the part of Clinical Trial Phase IV. | viii. A separate additional section is provided for the pharmacovigilance system for surveying and controlling the post approval undesired effects of the drug. |
| **Module 3** | |
| (i) The executed batch records for manufacturing and packaging are provided in Module 3.2.R for only single batch. | (i) The three executed batch records for manufacturing and packaging for Process validation schemes are provided in Module 3.2.R. |
| (ii) Information on components including the name and address of the supplier or manufacturer of the raw material, package material etc. provided in the 3.2.R | (ii) Information in components employed in the drug product formulations is generally not provided in the module 3.2.R |
| (iii) Letter of Access is not mentioned in 3.2.R. | (iii) Letter of access to Active substance master file of drug substance is provided for the agency. |
| (iv) TSE and BSE certificates are not attached in this section whereas submit in DMF. | (iv) TSE and BSE certificates are attached for drug substance and excipients. |
| (v) Certificate of suitability (CEP certificate) is not applicable. | (v) The latest Certificate of suitability (CEP) obtained from the EDQM Europe for each drug substance and excipients are attached. |

## CONCLUSION

The generic drug filings in the United States & Europe are the most demanding the world. The primary purpose of the rules governing medicinal products in US & Europe is to safeguard public health.

CTD provides a globally harmonized format that is accepted in many regions, avoiding the need to compile

different registration dossiers for different regulatory authorities. The primary purpose of the rules governing medicinal products in US is to check whether drugs are manufactured in accordance to the guidelines so that they are safe and patient's well-being is protected. Countries have different standards; there are high registration costs and long timelines for registration of generic drugs. This may account for the good market share of generics in USA and Europe.

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