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Documentation Requirements for Generic Drug Application to be Marketed in India- A Review

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ABSTRACT:

Branded drugs play an important role in medications, but generics are their cost effective alternatives. Generics are similar to branded drugs in terms of purity, efficacy and are perceived to be safer as compared to new drug molecules, as they tend to be older and time tested. Indian pharmaceutical market of generic drugs is increasing day by day. Indian pharmaceutical sector is rising very rapidly and there is a want of regulatory affairs professionals to provide the current needs of industries for the global competition. A regulatory affair is a somewhat new profession which has developed from the desire of governments to defend public health. Substantial documentation and data are required in these types of submissions, resulting in large, complex applications. Till date, applicants have used many different approaches in organizing the information and the differences in organization of data in each application has made reviewing more difficult and can also lead to omission of critical data or analyses. Such omissions can result in unnecessary delays in approvals. Thus, a common format of submission will help in overcoming these hurdles. Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance's have been developed for Japan, European Union, and United States. Thus, a brief discussion of the CTD guidelines has been presented in the article which is helpful for the marketing application for generic drugs in India.

KEYWORDS: Common Technical Document (CTD), Modules, Regulatory Requirements, Generic Drug Application

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INTRODUCTION:

1.1 Introduction to Regulatory Affairs[1]

Regulatory affairs (RA), also called government affairs, are a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory affairs also have a very specific meaning within the healthcare industries. Regulatory affairs is a comparatively new profession which developed from the desire of governments to protect public health by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines.

1.2 Introduction to Generic Drugs[2]

A generic drug (generic drugs, short: generics) is a drug defined as "a drug product that is comparable to brand/reference listed drug product in dosage form, strength, route of administration, quality and performance characteristics, and intended use. It has also been defined as a term referring to any drug marketed under its chemical name without advertising. 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.

A generic drug is identical--or bioequivalent--to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. Although generic drugs are chemically identical to their branded counterparts, they are typically sold at substantial discounts from the branded price.

- Opportunities arising from increased use of generics[3]

Ensuring the sustainability of the generic medicines industry is one of the key elements in maintaining broad access to medicines for all. To meet increasing demand from more patients who are living longer and expecting an improved quality of life, generic medicines offer quality treatment at affordable prices.

In order to ensure sustainability both investment in the generics sector and incentives for generic prescribing/dispensing are required in order to increase the market share of generics.

Driving first-line use

The development expertise within the generic medicines industry is recognised as being innovative. Furthermore, generic medicine companies have produced packaging specifically designed to help patients and minimize pharmacy dispensing errors. If the pressure is only on costs, without any incentive for advancements of this area, then the full potential of developments in this area will never be reached.

Unless rewarded, opportunities for further development will never be pursued and yet the benefits to patients could be significant.

Encouraging investment

Lack of flexibility in regulatory procedures and financial incentives puts European-based generic manufacturers at a disadvantage compared with the rest of the world.

The opportunity exists for governments to incentives the European generics medicine sector in order to generate a sustainable generics medicine industry. This will then be able to deliver cost savings through good patient management with high quality therapies at affordable prices.

- The Growth of Generics in India[4]

Inherent Competencies and Low-cost Manufacturing Capabilities

Indian pharmaceutical companies function on a much lower profit margin than their Western counterparts. Labour costs are between 50.0 per cent to 55.0 per cent cheaper than in the West. The cost of bulk drug production in India is 60.0 per cent lower, while the cost of setting up a production plant in India is 40.0 per cent lower than in the West.

Increasing Consolidation Through Co-operative Alliances

Mergers and acquisitions are common, and have helped Indian companies gain global market presence. Overall, generic companies with Indian headquarters have spent over $2.70 billion on mergers and acquisitions, since 2000.

Conducive Regulatory Environment

India currently has 75 United States FDA approved plants, enabling contract research and manufacturing services, and drug production as per the compliance requirements of developed countries. According to the WHO, more than 90.0 per cent of active pharmaceutical ingredient (API) approvals for anti-retro virus (ARVs), anti-tuberculosis treatments and anti-malarials were granted to India. As of January 2009,of the total 4,942 prequalified approvals granted by WHO, to 12 countries, India has 621 approvals for six companies.

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)[5]

ICH stands for International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

ICH is a joint initiative involving both regulators and research-based industry representatives of the EU, Japan and the US in scientific and technical discussions of the testing procedures required to assess and ensure the safety, quality and efficacy of medicines.

ICH's mission is to make recommendations towards achieving greater harmonisation in the interpretation and application of technical Guidelines and requirements for pharmaceutical product registration.

ICH is comprised of representatives from the six cosponsoring parties as well as three Observers and the International Federation of Pharmaceutical Manufacturers Associations (IFPMA):

Japan: the Ministry of Health & Welfare (MHW) and the

Japan Pharmaceutical Manufacturers Association (JPMA)

EU: the European Commission (EC) and the European

Federation of Pharmaceutical Industries' Associations (EFPIA)

USA: the Food & Drug Administration (FDA) and the

Pharmaceutical Research and Manufacturers of America (PhRMA)

1.3 The Common Technical Document (CTD)[6]

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 is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries. 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)(As shown in figure1).

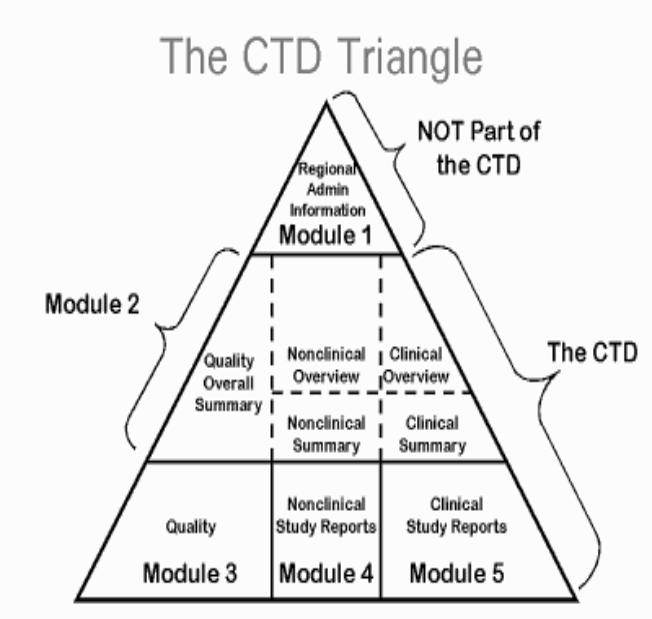

Figure 1: CTD triangle [7]

The Common Technical Document is divided into five modules:

Administrative and prescribing information

Overview and summary of modules 3 to 5

Quality (pharmaceutical documentation)

Preclinical (Pharmacology/Toxicology)

Clinical - efficacy (Clinical Trials)

1.4 Indian Generic Pharmaceuticals Market[8]

India is primarily a branded generics (molecular copy of an off-patent drug with a trade name) market. However, it is important to note that generic versions of molecules which still had patent protection in the rest of the world were produced (by reverse engineering) and marketed in India by domestic market participants until 2005, since India did not follow any patent protection laws up to 2005. Hence, the Indian generic market size includes the sales value of generic drugs sold by both big pharma companies (generic copies of the innovator's molecule sold under a different trade name) as well as Indian generic companies.

The Indian pharmaceutical industry, which is the third largest globally in terms of volume, had a total production output of $23.24 billion in 2010, and was the thirteenth largest, in terms of value. The domestic Indian pharmaceutical market was worth $12.24 billion in 2010, and grew at a significant rate of 17.0 percent per year.

- COMPARISON ON REGULATORY REQUIREMENT FOR GENERICS BETWEEN US, INDIA AND EUROPE[9] (shown in table 1).

Table 1 Comparison on regulatory requirements for generics between US, INDIA and Europe[9]

ADMINISTRATIVE		**USA**	**INDIA**	**EUROPE**
1.	Application	ANDA	MAA	MAA
2.	Debarment certification	Required	NA	NA
3.	No. of copies	3	1	1
4.	Approval timeline	18month	12month	12month
5.	Presentation	e-CTD	Paper	Paper+CTD

Documents in each Module (As per table 2)

Table 2 Modules[10]

Module	Information
1	Administrative and prescribing information (region specific)
2	Summaries and overview
3	Information on product quality
4	Nonclinical study reports
5	Clinical study reports

1.5.GENERAL CONSIDERATIONS FOR DOSSIER PREPARATION[11]

The CTD is only a format for submission of information to CDSCO.

Although adherence to overall CTD structure is necessary, it should be noted that no guideline can cover all eventualities, and common sense and a clear focus on the needs of the regulatory authority assessor are the best guides to constructing an acceptable document. Therefore, applicants can modify the format at some of the subsection levels, if needed to provide the best possible presentation of the information, in order to facilitate the understanding and evaluation.

Text and tables should be prepared using margins that allow the document to be printed clearly without losing any information and the left-hand margin should be sufficiently large so that information is not obscured by the method of binding.

Font sizes for text and tables should be of a style and size that are large enough to be easily readable. Times New Roman, 12-point font is recommended for descriptive text and Times New Roman, 9 to 10-point font for table contents and text.

All abbreviations should be defined at the first instance they are used and listed at the end of the dossier.

References should be cited in accordance with the current edition of the uniform requirements for manuscripts submitted to biomedical journals , International Committee of Medical Journal Editors (ICMJE).

1.6 GUIDELINES FOR PREPARATION OF CTD

Module 1: General Information

This module should contain documents specific to India; for example, Form 44, Treasury challan fee or the proposed label for use in India.

CRITICAL SECTIONS UNDER MODULE 1:

- Duly filled and signed application in Form 44 and Treasury Challan
- Legal and Critical Documents:

  A. Copy of Clinical Trial/BE No Objection letters issued by CDSCO

  B. Copies of any other relevant competent authority clearances/ approvals / no objection certificates obtained or any key communication letters with authorities.
- Certificate of Analysis
- Coordinates related to the application
- General information on drug product:

  A. A brief description of the drug and the therapeutic class to which it belongs

  B. Dosage form

  C. Dispensing requirements

  D. Full Prescribing Information

  E. Product Labelling: Proposed draft labels and cartons have to be provided. Module 2: CTD Summaries

This module should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use, not exceeding one page. Module 2 should contain 7 sections in the following order(As given in table 3)

SR NO.	CONTENTS
2.2	**Introduction to Summary**
2.3	**Quality Overall Summary**
2.3.S	**Summary of Drug Substance**
2.3.P	**Summary of Drug Product**
2.4	**Non Clinical Overview**
2.5	**Clinical Overview**
2.6	**Non Clinical written and tabulated Summaries**
2.7	**Clinical Summary**

Table no 3: Contents of module 2

CRITICAL SECTIONS UNDER MODULE 2:

Introduction: This should include proprietary name, non-proprietary name or common name of the drug substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s).

Quality Overall Summary

Summary Of Drug Substance:

General Information

Characterisation

Container Closure System

Stability

Summary Of Drug Product

Reference Standards or Materials

Stability

Container Closure System

Pharmacodynamics

Pharmacokinetics

Toxicology

Clinical Overview

Non Clinical Overview

Module 3: Quality

Information on Quality should be presented in the structured format according to all the subsections of Quality guidelines(As given in table 4).

SR NO.	CONTENTS
3.2.S	**DRUG SUBSTANCE**
3.2.S.1	**GENERAL INFORMATION**
	3.2.S.1.1 Nomenclature
	3.2.S.1.2 Structure
	3.2.S.1.3 General Properties
3.2.S.2	**MANUFACTURE OF DRUG SUBSTANCE**
	3.2.S.2.1 Manufacturer(s)
	3.2.S.2.2 Description of Manufacturing process and process controls
	3.2.S.2.3 Control of materials
	3.2.S.2.4 Controls of critical steps and Intermediates
	3.2.S.2.5 Process Validation and/or Evaluation
	3.2.S.2.6 Manufacturing Process Development
3.2.S.3	**CHARACTERIZATION OF DRUG SUBSTANCE**
	3.2.S.3.1 Elucidation of structure and other characteristics
	3.2.S.3.2 Impurities
3.2.S.4	**QUALITY CONTROL OF DRUG SUBSTANCE**
	3.2.S.4.1 Specification and Justification of specification
	3.2.S.4.2 Analytical Procedures
	3.2.S.4.3 Validation of Analytical Procedures
	3.2.S.4.4 Batch Analyses
3.2.S.5	**REFERENCE STANDARDS OR MATERIALS**
3.2.S.6	**CONTAINER CLOSURE SYSTEM**
3.2.S.7	**STABILITY OF DRUG SUBSTANCE**
	3.2.S.7.1 Stability summary and conclusions
	3.2.S.7.2 Post approval stability protocol and Stability commitment
	3.2.S.7.3 Stability data
3.2.P	**DRUG PRODUCT**
3.2.P.1	**DESCRIPTION AND COMPOSITION OF DRUG PRODUCT**
3.2.P.2	**PHARMACEUTICAL DEVELOPMENT**
	3.2.P.2.1 Components of drug product
	3.2.P.2.1.1 Drug Substance
	3.2.P.2.1.2 Excipients
	3.2.P.2.2 Drug Product
	3.2.P.2.2.1 Formulation development
	3.2.P.2.2.2 Overages
	3.2.P.2.2.3 Physicochemical and biological properties
	3.2.P.2.3 Manufacturing process Development
	3.2.P.2.4 Container Closure System
	3.2.P.2.5 Microbiological Attributes
	3.2.P.2.6 Compatibility
3.2.P.3	**MANUFACTURE OF DRUG PRODUCT**
	3.2.P.3.1 Manufacturer(s)
	3.2.P.3.2 Batch Formula
	3.2.P.3.3 Description of Manufacturing process and process controls
	3.2.P.3.4 Controls of critical steps and Intermediates
	3.2.P.3.5 Process Validation and/or Evaluation
3.2.P.4	**CONTROL OF EXCIPIENTS**
	3.2.P.4.1 Specifications and Justification of Specifications
	3.2.P.4.2 Analytical Procedures
	3.2.P.4.3 Validation of Analytical procedures
	3.2.P.4.4 Excipients of human or animal origin
	3.2.P.4.5 Excipients used for the first time
3.2.P.5	**CONTROL OF DRUG PRODUCT**
	3.2.P.5.1 Specifications and Justification of Specificati
	3.2.P.5.2 Analytical Procedures
	3.2.P.5.3 Validation of Analytical procedures
	3.2.P.5.4 Batch Analyses
	3.2.P.5.5 Characterisation of Impurities
3.2.P.6	**REFERENCE STANDARDS OR MATERIALS**
3.2.P.7	**CONTAINER CLOSURE SYSTEM**
3.2.P.8	**STABILITY OF DRUG SUBSTANCE**
	3.2.P.8.1 Stability summary and conclusions
	3.2.P.8.2 Post approval stability protocol and Stability
	3.2.P.8.3 Stability data

Table no 4: Contents of module 4

CRITICAL SECTIONS UNDER MODULE 3:

- Body Of Data:

A. Drug Substance: Structure, General properties, Description of manufacturing process and process controls, Control of critical steps, Process validation, Impurities, Quality Control of drug substance, Reference standards, Container closure system, Stability Data. B. Drug Product: Description and composition of drug product, Pharmaceutical development,

Physicochemical and biological properties, Excipients, Microbiological Attributes, Batch formula, Analytical Procedures, Control of Excipients.

Module 4: Nonclinical Study Reports

The nonclinical study reports should be presented.

For Generic drugs complete non clinical study is not required to be shown as the safety data are already proved during the approval of the branded drugs.

Module 5: Clinical Study Reports

The human study reports and related information should be presented.

CONCLUSION:

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Globalization of the pharmaceutical industry has created the need to harmonize the recommendations for the development of new pharmaceuticals, as well as the regulatory requirements of various countries. Substantial documentation and data are required in these types of submissions, resulting in large, complex applications. Thus, a common format of submission will help in overcoming these hurdles. In India, CDSCO adopted CTD format for technical requirements for registration of pharmaceutical products in 2009-2010.Still inspite of the CDSCO approval, there are certain companies that do not have knowledge about the primary requirements for preparation of dossier according to the CTD format.

Since CDSCO guidelines made the filing of a dossier in CTD format compulsory in India, the above study emphasizes on how to prepare a dossier according to the CTD.

Generic Drug market is a vast and cost effective market for all the developing pharmaceutical companies. Hence, the study was chosen keeping greater emphasis on the current scenario of generic drug market and regulations for generic drug manufacturing as well as marketing.

Hence, the purpose of this work is to gather knowledge about various technical document requirements and also study of various guidelines supporting the generic drug filing process.

Since CDSCO guidelines made the filing of a dossier in CTD format compulsory in India, the above study emphasizes on how to prepare a dossier according to the CTD.

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