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REGULATORY REQUIREMENTS FOR MARKETING OF GENERIC DRUGS IN USA

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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. The availability of generic medication is an important issue in the ASEAN region. The regulatory requirements of various countries vary from each other. Therefore it is challenging for the companies to develop a single drug which can be simultaneously submitted in various countries for approval. The role of regulatory authorities is to ensure the quality, safety, and efficacy of all medicines in circulation in their country. It not only includes the process of regulating and monitoring the drugs but also the process of manufacturing, distribution, and promotion. The regulatory environment has similar characteristics but drug registration requirements and processes differ among the countries. One of the primary challenges for regulatory is to ensure that the pharmaceutical products are developed as per the regulatory requirement of that country. This process involves the assessment of critical parameters during product development. Regulatory requirements and generic drug registration for USA and ASEAN regions is made at the end of the section. In ASEAN region documentation can be filed in the ACTD format. In US region documentation can be filled in the CTD/eCTD format.

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

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INTRODUCTION

1.1. Introduction to Regulatory Affairs

Regulatory affairs (RA), also called **government affairs**, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, banking, telecom etc. Regulatory affairs also has a very specific meaning within the healthcare industries (Pharmaceuticals, Medical devices, Biologics and Functional foods). The regulatory function in healthcare industries is vital in making safe and effective healthcare products available worldwide. Individuals who ensure regulatory compliance and prepare submissions, as well as those whose main job function is clinical affairs or quality assurance are all considered regulatory professionals [1].

Regulatory professionals are employed in industry, government and academia and are involved with a wide range of products, including [2]:

- pharmaceuticals
- medical devices
- in vitro diagnostics
- biologics and biotechnology
- nutritional products
- cosmetics
- veterinary products

The regulatory professional's roles and responsibilities often begin in the research and development phases, moving into clinical trials and extending through premarket approvals, manufacturing, labeling and advertising and post market surveillance.

1.2. Introduction to Generic Drugs

A generic is a drug defined as a drug substance that is resemblance to brand/reference listed drug product in dosage form, quality strength and performance characteristics, I tended use and route of administration. In the other way there are solid with their chemical nature without advertising. Even though they are similar in their nature they vary in their cost. The generic drugs go for the sale in low cost. Moreover the percentage of generic drug user are also

increasing. The generic drugs offer quality treatmentto meet such demands in low cost. The requirements to develop the generic drugs are incentives [3].

1.3. Rapid Growth of Generic Drugs in U.S

The generics industry quickly put this setback behind it. In 1984, generic drugs were just 19% of prescriptions in the U.S., according to the market research firm IMS Health. By 2013, they had reached 86%.

"Among first-line treatment alternatives, nearly every therapeutic class and disease state currently has at least one generic medicine available," points out Sigurdur Olafsson, chief executive officer of Teva Pharmaceutical Industries' global generic medicines group. Israel's Teva, which sells both generic and brand-name drugs, leads the generic drug industry in sales, followed closely by Sandoz, the generics arm of Switzerland's Novartis [4].

In the U.S., generics have become "the pillar of health care," says Peter Goldschmidt, president of Sandoz U.S. As such, "we have a responsibility to ensure, together with the FDA, that high-quality medicines come into this country or are produced here."

According to the Generic Pharmaceutical Association, the U.S. has saved nearly $1.5 trillion over the past 10 years by having inexpensive generic alternatives to high-priced branded drugs. It's a result that no one could have predicted 30 years ago, says the trade group's CEO, Ralph G. Neas. "The Hatch-Waxman law has yielded hundreds of unprecedented medical breakthroughs by rewarding innovation and trillions of dollars in savings from encouraging competition."

Although Hatch-Waxman accelerated the speed at which generics come to market in the U.S., its impact has been global. "We are seeing ourselves in a far more generic world," says Alan Sheppard, IMS Health principal for generics [5].

In 2012, global generics sales reached $260 billion. And the market is predicted to experience double-digit annual growth through 2017. A large number of patent expirations and a push by countries toward affordable medicines are among the drivers of recent growth, Sheppard adds.

Although sales of generics are only a quarter as large as those of patented drugs because of generics' significantly lower prices, those sales are growing at least twice as fast. In recent years FDA has been approving about four times the number of Abbreviated New Drug Applications (ANDAs) for generics compared with applications for brand-name drugs.

Behind the increase is a significant shift in the sources of those applications toward Indian firms, says Molly Bowman, senior manager at the research firm Thomson Reuters. In the 1990s, companies from the U.S., Israel, and a few other countries were heavily represented in the U.S.

generics market, but that has shifted to include many other parts of the world, Bowman explains.

In 1990, about 50% of ANDAs came from U.S. firms and 15%, from India. By 2012, U.S. company filings had dropped to 30% and Indian ones had grown to 40%. Over the past 10 years, Indian filings have risen to around 200 per year, while the companies involved have increased fivefold to about 25. Generic drugs now account for the bulk of prescriptions in the U.S [6]

1.4. Consolidating Generic drugs sector in U.S Sector

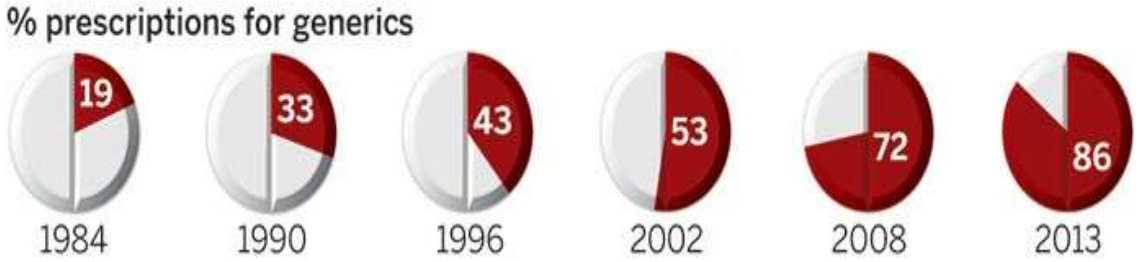

Fig-1-Generic drugs now account for the bulk of prescriptions in the U.S

1.4. The Common Technical Document (CTD) [7]

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 figure2).

The Common Technical Document is divided into five modules [8]:

1. Administrative and prescribing information

2. Overview and summary of modules 3 to 5

3. Quality (Pharmaceutical documentation)

4. Preclinical (Pharmacology/Toxicology)

5. Clinical - efficacy (Clinical Trials)

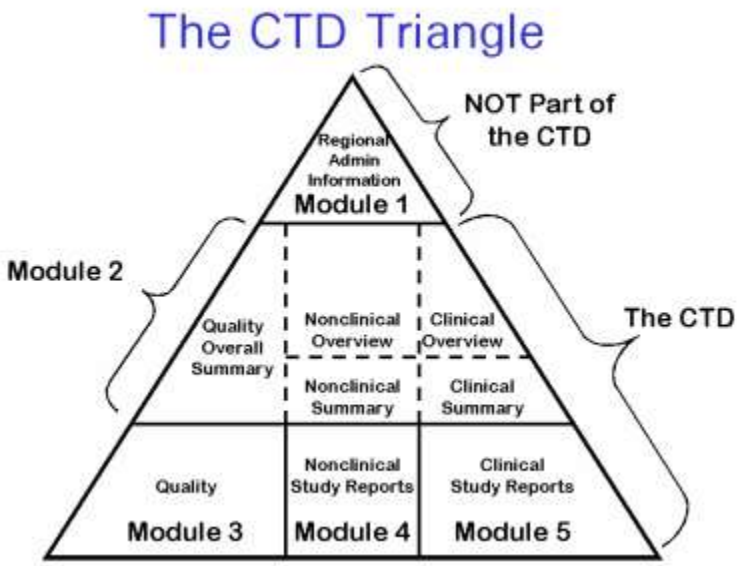

Fig-2- The CTD Triangle

1.5. USA Generic Pharmaceuticals Market [9]

The U.S. Generic industry continued to experience dramatic growth in2015as the share of generic prescriptions approaches90%,driven by an unprecedented set of recent patent expirations. The US generic drug market has witnessed a transformation over the last three decades. From less than 20% of the total prescriptions, generic drugs now account for the majority of the total prescriptions dispensed in the United States. During 2010-2015, the US generic drug market grew at a CAGR of more than 11% and currently represents a multibillion dollar industry. The biggest catalyst of this industry is the significantly lower price of generics compared to branded drugs.

The U.S. prescription generic drug market is projected to grow from an estimated $11.1 billion in 2001 to more than $19 billion in 2006, representing an average annual growth rate (AAGR) of 11.4%.

The generics drug market is projected to enjoy double-digit growth throughout the forecast period, Generics represent a lesser percent of prescriptions written in most other countries but are gaining share almost universally. In 2001, generics represented approximately 11% of the international pharmaceutical market and 9% of the U.S. drug market in dollars compared to 6% growth projected for branded products [10].

	FY2015	FY2016	FY2017
Original ANDA	60% in 15 months	75% in 15 months	90% in 10 months
Tier 1 first major amendment	60% in 10 months	75% in 10 months	90% in 10 months
Tier 1 minor amendments (1st–3rd)	60% in 3 months	75% in 3 months	90% in 3 months
Tier 1 minor amendments (4th-5th)	60% in 6 months	75% in 6 months	90% in 6 months
Tier 2 amendments	60% in 12 months	75% in 12 months	90% in 12 months
Prior approval supplements	60% in 6 months	75% in 6 months	90% in 6 months
ANDA teleconference requests	Close-out 200	Close-out 250	Close-out 300
Controlled correspondences	60% in 4 months	70% in 2 months	90% in 2months

Fig-3- Implementation of the Generic Drug User Fee Amendments of 2012 (GDUFA)

1.6. GENERAL CONSIDERATIONS FOR DOSSIER PREPARATION [11-16]

Drug Master File (DMF) is a submission to the Food and Drug Administration (FDA) that maybe used to provide confidential detailed information about facilities, processes, or articles used in the manufacturing, processing, packaging, and storing of one or more human drugs. The information contained in the DMF may be used to support following,

– Investigational New Drug Application (IND),

– New Drug Application (NDA),

– Abbreviated New Drug Application (ANDA),

– Export Application.

An Abbreviated New Drug Application (ANDA) is an application for a U.S. generic drug approval for an existing licensed medication or approved drug. The ANDA contains data which when submitted to FDA's Center For drug Evaluation and Research (CDER), 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.

Module-1: Administrative Information and Prescribing Information

1.0 Cover Letter

1.1 Comprehensive Table of Content

1.2 Application Form

1.3 Product Information

1.3.1 SPC's, Labelling and Packaging

1.3.2 Mock-Up

1.3.3 Specimen

1.3.4 Consultation with target patient group

1.3.5 SPC's already approved in the Member states

1.3.6 Braille

1.4 Information about the Experts

1.5 Specific Requirements for different types of applications

1.6 Environmental Risk Assessment

1.7 Information relating to Orphan Market Exclusivity

1.8 Information relating to Pharmacovigilance

1.9 Information relating to Clinical Trials

1.10 Information relating to Pediatrics

1.11 Response to Queries

1.12 Additional Data

Module - 2: CTD Summary

2.1 Table of Content (Comprehensive)

2.2 Introduction (general introduction to the pharmaceutical, including its pharmacology class, mode of action, and proposed clinical use)

2.3 Quality Overall Summary

2.4 Non-clinical Overview

2.5 Clinical Overview

2.6 Non-clinical Written and Tabulated Sum2.4 Non-clinicalOverview

2.4.1 General Aspects

2.4.2 Content and Structural Format

2.5 Clinical Overview

2.5.1 Product Development of Content Rationale

2.5.2 Overview of Biopharmaceutics

2.5.3 Overview of Clinical Pharmacology

2.5.4 Overview of Efficacy

2.5.5 Overview of Safety

2.5.6 Benefits and Risks Conclusions

2.5.7 Literature Referencesmaries

2.7 Clinical summary

2.6 Non-clinical Written and Tabulated Summaries

2.6.1 Pharmacology

2.6.2 Pharmacokinetics

2.6.3 Toxicology

2.7 Clinical summary

2.7.1 Biopharmaceutic Studies and Associated

Analytical Methods

2.7.2 Clinical Pharmacology Studies

2.7.3 Clinical Efficacy

2.7.4 Clinical Safety

2.7.5 Literature References

Module – 3: Quality

3.1 Table of Contents

3.2 Body of Data

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

3.2.S.2.1 Manufacturer Details

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 Characterisation

3.2.S.3.1 Elucidation of structure and other Characteristics

3.2.S.3.2 Impurities

3.2.S.4 Control of Drug Substance

3.2.S.4.1 Specification of Drug Substance

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.4.5 Justification of Specification

3.2.S.5 Reference Standards or Materials

3.2.S.6 Container Closure System

3.2.S.7 Stability

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 the Drug

Product

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of Drug Product

3.2.P.2.2 Drug Product

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

3.2.P.3.1 Manufacturer

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.3.2.P.4.1 Specifications

3.2.P.4.2 Analytical Procedures

3.2.P.4.3 Validation of Analytical Procedures

3.2.P.4.4 Justification of Specifications

3.2.P.4.5 Excipients of Human or Animal Origin

3.2.P.4.6 Novel Excipients

3.2.P.Control of Drug Product

3.2.P.5.1 Specification of Drug Product

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.5.6 Justification of Specification

3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusions

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

3.2.P.8.3 Stability Data

3.2.A Appendices

3.2.A.1 Facilities and Equipment

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.3 Novel Excipients

3.2.R Regional Information/ Requirements

3.2.R.1 Process Validation and or Evaluation

3.2.R.2 Medical Device

3.2.R.3 Restricted part of DMF

3.2.R.4 Medicinal products containing or using in the manufacturing process materials of animal and / or human origin.

3.3 List of Literature References

Module - 4: Non-clinical Study Reports

4.1 Table of contents

4.2 Study Reports

4.2.1 Pharmacology

4.2.1 Primary Pharmacodynamic

4.2.2 Secondary Pharmacodynamic

4.2.3 Safety pharmacology

4.2.4 Pharmacodynamic drug interactions

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and validation Reports

4.2.2.2 Absorption

4.2.2.3 Distribution

4.2.2.4 Metabolism

4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions

4.2.2.7 Other Pharmacokinetic studies

4.2.3 Toxicology

4.2.3.1 Single-dose toxicity

4.2.3.2 Repeat-dose toxicity

4.2.3.3 Genotoxicity

4.2.3.4 Carcinogenicity

4.2.3.5 Reproductive and developmental toxicity

4.2.3.6 Local tolerance

4.2.3.7 Other toxicity studies

4.3 Literature References

Module - 5: Clinical Study Reports

5.1 Table of Contents

5.2 Tabular Listings of All Clinical Studies

5.3 Clinical Study Reports

5.3.1.1 Bioavailability (BA) study Reports

5.3.1.2 Comparative BA and Bioequivalence study reports

5.3.1.3 In-vitro In-vivo Correlation study reports

5.3.1.4 Reports of Bioanalytical and Analytical methods

5.3.2.1 Plasma Protein Binding Study Reports

5.3.2.2 Reports of Hepatic metabolism and Drug Interaction Studies

5.3.2.3 Reports of Studies Using human Biomaterials

5.3.3.1 Healthy Subject PK and Initial Tolerability study reports

5.3.3.1 Healthy Subject PK and Initial Tolerability study reports

5.3.3.2 Patient PK and Initial Tolerability study reports.

5.3.3.3 Intrinsic Factor PK study reports

5.3.3.4 Extrinsic Factor PK study reports

5.3.3.5 Population PK study reports

5.3.4.1 Healthy subject PD and PK/PD study reports

5.3.4.2 Patient PD and PK/PD study reports

5.3.5.1 Study reports of controlled clinical Studies

5.3.5.2 Study reports of Uncontrolled clinical studies

5.3.5.3 Reports of Analyses of data from more than one study

5.3.5.4 Other clinical study reports

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case report forms and Individual patient listings

5.4 List of Key Literature References

2. MARKETING A DRUG PRODUCT IN USA [17]

To enter into the US market, the product will need to get the approval from the US Food and Drug Administration (FDA). The applicant files a market application with FDA. After reviewing the application, FDA will decide whether to grant the product approval. Selling the product without the approval would make you a felony under the US Federal Food, Drug and Cosmetic Act.

2.1. The FDA has approved following pathways [17]:

1. The Abbreviated New Drug Application (ANDA),

2. Over-the-Counter (OTC) Monograph

3. The New Drug Application (NDA).

Generic Drug Product Registration Requirements in US

1. The eCTD is mandatory for the submission of the drug applications (NDA/ANDA).

2. US FDA guidance (CFR) documents and FDA sections (e.g. 505 (b) for NDA and 505(j) for ANDA) are followed for the preparation of the dossier for the drug approval applications.

3. The applications are different

e.g. For new drug- NDA

For generic drug – ANDA

For biological application – BLA

4. The application is directly submit to the FDA by the applicant or through any approved contact agent for whom a certification is provided to the agency according to the GDEA 1992.

5. Administrative information is different i.e. cover letter, forms (356h), application information, field copy certification, debarment certification, financial certification, Patent information and exclusivity.

6. 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.

7. Package inserts are provided for drug product in labeling.

8. Proposed Labels and cartons with proper dimensions similar to that of the RLD labels are provided.

9. The information about the clinical investigators is provided in the Module 5 and in financial disclosure Statement section of this module.

10.Request for waiver of in-vivo BE studies is provided in the module 1.

11.Annotated draft labeling (side by side) for labels and cartons compared with the RLD with proper annotation is provided.

12.The EAS (Environment Assessment Statement) for categorical exclusion certification in compliance with the law of EPA of US is provided.

13.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.

14.The executed batch records for manufacturing and packaging are provided in Module 3.2.R for only single batch.

15.The declaration is given for the residual solvents limits used or present in the drug substance and excipients according to the USP.

16.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.

17.Letter of Access is not mentioned in 3.2.R.

18.Transmissible Spongiform Encephalopathy (TSE) and Bovine Spongiform Encephalopathy (BSE) certificates are not attached in this section whereas submit in DMF.

19.Certificate of suitability (CEP certificate) is not applicable.

20.Comparability protocols are not attached for both the drug substance and drug products.

21.The stability data for accelerated studies are submitted for three months at the time of original submission.

22.Node extension is not allowed in the eCTD XML in software.

23.Structured product labeling (SPL) and study tagging file (STF) is mandatory by the USFDA in eCTD of a drug registration application. Paper CTD format is not accepted by FDA at all.

For the registration of generic drugs in USA we should follow the ANDA regulatory review process.

2.2. ANDA Regulatory Review Process [17]

The ANDA process begins when an applicant submits an ANDA to the OGD. The document room staff process the ANDA assigns it an ANDA number, and stamps a received date on the cover letter of the ANDA. The ANDA is then sent to a consumer safety technician, who reviews the preliminary sections of the ANDA checklist. Within the first 60 days following the submission of an ANDA, a filing review is completed.

3. SUMMARY & CONCLUSION

The generic drug filing in the United States is the most demanding in the world. The primary purpose of the rules governing medicinal products in US is to safeguard public health. It is the role of public regulation authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well – being is protected. CTD provides a globally harmonised 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.

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