

**DOSSIER SUBMISSION PROCESS IN EUROPE AND UNITED STATES****Dnyaneshwar Mali\*<sup>1</sup> and Dr. S.V. Desphande<sup>2</sup>**<sup>1</sup>Regulatory Affair Officer, Medisel Kenya Ltd, Ahmedabad.<sup>2</sup>Principal Dr Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research.Article Received on  
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**ABSTRACT**

Current oblige of Regulatory Affairs reveals diverse countries need to follow different regulatory requirements for marketing authorization Application (MAA) approval of new drugs. In this present effort, study expresses the drug approval process and regulatory requirements according to US Food and Drug Administration (USFDA), European Medical Agency (EMA). Generic drugs in EU are endorsed under the Marketing Authorization Application. Medicinal products are highly monitored in the European Union (EU) and are subject to a separate, complicated system of approvals that governs how, when, where, and in what form such products will be allowed to be sold within the

borders of EU. USFDA is one the most regulated agencies wherein the submission process is hairsplitting. A Generic Product must satisfy the guidelines built up by FDA in RLD (Reference listed drug).

**KEYWORDS:** Generic drugs, Marketting approval, European Medical Agency.**1) INTRODUCTION**

For the approval of drug product, file of document have to submit which is known as dossier. It is submitted in the form of CTD. In ICH region they have one common format through which data on drug product is presented is called CTD. The generic product is comparable to innovator product in various properties like in dosage form, strength, quality.

In the English dictionary for the collection of files for the same product is called as Dossier, which contains all the information in detail for particular. Pharmaceutical product for human use is which explore physiological systems or pathological systems for the benefit of the humans or recipient.

After submission of dossier which contains all details is evaluated for the details like administrative data, clinical, pre-clinical data, and chemistry and after that if it is found efficient then by the regulatory authority gives approval which is called as marketing approval. Marketing approval also known as product licensing.<sup>[1]</sup>

In the European Union (EU) Medicinal products are highly regulated and are complicated system of approvals that governs how, when, where, and in what form such products will be allowed to be sold within the borders of the EU.<sup>[2]</sup>

The European Union, comprises 27 Member States. They continuously worked on developing and streamlining drug review and marketing authorization processes. 3 different procedures are can be used to submit a medicinal product for marketing approval in the European Union. In this review we are focusing on the available avenues and describe when one might be used over another.<sup>[3]</sup>

It is believed that approval of new drug in the United States has world's most stringent standards. In the United States most demanding thing which is considered by many in the world is drug approval.

Assurance and advancing of general wellbeing of United States individuals is the primary duty of The Food and Drug Administration (FDA). FDA's new medication endorsement process is additionally experienced through two stages: clinical trials (CT) and New Drug Application (NDA) approval. When the Investigational New Drug (IND) application is submitted with the required reports then just approval process starts.<sup>[4]</sup>

## **2) Types of marketing authorization procedure/Dossier submission process<sup>[5]</sup>**

Before getting marketing approval in Europe there are two process through which applicants have to process. These are clinical trial and marketing authorization. The four described procedures are published by the European Commission in consultation with the competent authorities of the Member States, the European Medicines Agency (EMA), and interested parties.

- 1) Mutual Recognition Procedure (MRP)
- 2) Decentralized Procedure (DCP)
- 3) Centralized Procedure (CP)
- 4) National procedure

### 1) Centralized procedure

When application is made through The centralized procedure applicants to obtain a marketing authorization that is valid throughout the EU.

- Results in a single authorization valid in EU, Norway, Iceland and Liechtenstein.
- Application evaluated by an assigned Rapporteur.
- Timeline: EMA opinion issued within 210 days, and submitted to European Commission for final approval

### Centralized process is compulsory for

Medicines which are derived under following category

- any biotechnology processes, such as genetic engineering.
- intended for the treatment of Cancer, HIV/Aids, diabetes, neurodegenerative disorders or autoimmune diseases and other immune dysfunctions.
- orphan medicines' (medicines used for rare diseases).

### 2) Mutual recognition procedure

Under the Mutual recognition procedure applicants possess marketing approval in the member states (Concerned Member State) other than the member state (Reference Member State) where the drug is previously approved.

- Applicant submits identical dossier to all EU member states in which it wants authorization, including required information.
- As soon as one Member State decides to evaluate the medicinal product (at which point it becomes the "RMS"), it notifies this decision to other Member States (which then become the "CMS"), to whom applications have also been submitted.
- RMS issues a report to other states on its own findings.
- Generic industry is the major user of this type of drug approval procedure.
- This process may consume a time period of 390 days.

### 3) Nationalized procedure

When applicant submit application under The Nationalized procedure applicant get a marketing authorization in one member state only.

An application must be submitted to the competent authority of the Member State, in order to obtain a national marketing authorization,

New API substances which are not mandatory under Centralized procedure can obtain marketing authorization under this procedure.

210 Days is a timeline for this procedure.

#### **4) Decentralized procedure**

Using this procedure, companies may apply for authorization simultaneously in more than one EU country for products that have not yet been authorized in any EU country and essentially do not fall within the centralized procedure's essential drugs list. Based on the assessment report which is prepared by the RMS& any comments made by the CMS, MA should be granted in accordance with the decision taken by the RMS&CMS in this decentralized procedure.

Generally used for those products that has not yet received any authorisation in an EU country.

Timeline is 210 days.

### **3) What is Marketing Authorisation in europe**

Marketing authorization has issue by the competent regulatory authority in EEA and then only a medicinal product may only be placed on the market in the European Economic Area (EEA). The applicant who got the The marketing authorisation must be established within the EEA<sup>[3]</sup>

### **3) Dossier submission Procedure in USA**

#### **Investigational New Drug (IND) Application**

It's an application recorded to the FDA so as to begin clinical preliminaries in people if the medication was observed to be sheltered from the reports of Preclinical preliminaries. A firm or foundation, called a Sponsor, is in charge of presenting the IND application. A pre - IND meeting can be masterminded with the FDA to talk about various issues:

- The structure of creature look into, which is required to loan support to the clinical investigations.
- The proposed convention for directing the clinical.
- The science, assembling, and control of the investigational sedate

Such a gathering will assist the Sponsor with organizing creature explore, assemble information, and structure the clinical convention dependent on recommendations by the FDA.<sup>[5]</sup>

### **ANDA (Abbreviated New Drug Application) Filing Requirement**

An Abbreviated New Drug Application (ANDA) is an application for U.S. generic tranquilize endorsement for a current authorized medicine or affirmed medication. The ANDA contains information which when submitted to FDA's Center for Drug Evaluation and Research (CDER) office, office of nonexclusive medication, accommodates the survey and extreme endorsement of a conventional medication item. When affirmed, a candidate may fabricate and advertise the conventional medication item to give a safe, compelling, ease option in contrast to the American open.

### **ANDA Forms**

In order to submit a complete ANDA, applicants should review the following forms and prepare all that are required for your specific application.

- Filing Review of ANDAs MAPP including filing checklist
- Form FDA-356h: Application to Market a New Drug, Biologic, or Antibiotic Drug for Human Use
- Instructions for using Form FDA-356h Form FDA-3794: GDUFA Cover Sheet
- Instructions for creating a GDUFA Cover Sheet
- Form FDA-3674: Certification of Compliance
- Instructions for completion of Form FDA-3674
- Generic Drug User Fee Payment Information
- Drug Master Files (DMFs)

### **Requesting a Pre-Assigned ANDA Number**

Registrant may request a pre-assigned ANDA number ONLY when submitting a new ANDA. If you are converting an established ANDA to eCTD, you MUST use the original ANDA application number. For further guidance, please view Requesting a Pre-Assigned ANDA Number

### **Electronic Submissions**

This is CTD structure which is submitted in the eCTD in the ANDA accommodation for FDA This is set up as following the ICH rule.

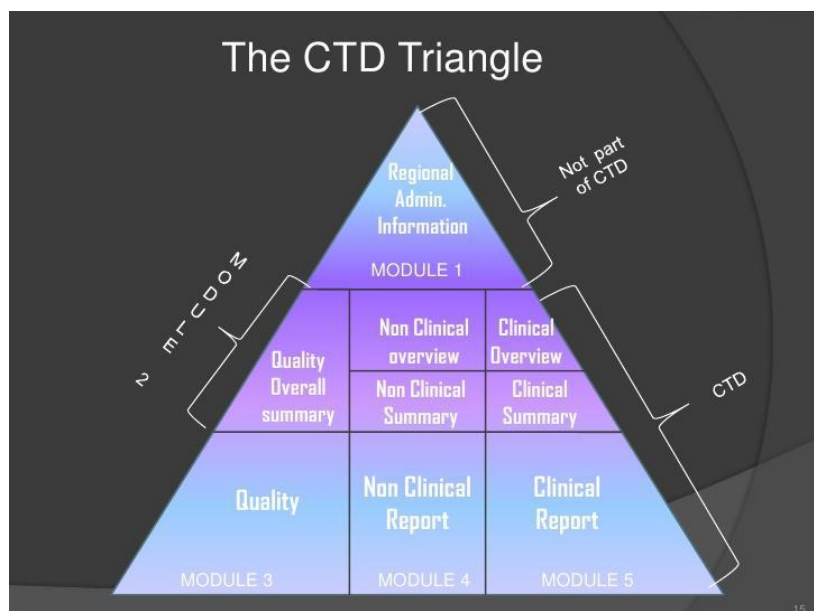


Figure No 1.Ctd Format Describes Module<sup>[6]</sup>

### Modules in CTD

Dossiers are submitted in CTD format. There are 5 sections in CTD. These are called as Modules. These are as per below

Module I: Administrative and Prescribing Information.

Module II: Summaries and Overviews.

Module III: Quality Documents.

Module IV: Non-Clinical Study Reports

Module V: Clinical Study Reports

### Module I: Administrative and Prescribing Information

1. Table of Contents.
2. Includes data of Administrative Documents entailing: Patent Information on patented product, Patent Certifications, Debarment certification.
3. Prescribing information like Package and container labels, packaging inserts, patient leaflets, etc.
4. Labelling Comparison between Innovator and Generic drug.

### Module II: Summaries and Overviews

1. Table of Contents.
2. Introduction to Summary Documents.
3. Overviews and Summaries: Module II should contain documents like:

- M4Q: The CTD- quality
- M4S: The CTD- safety

***Module III: information on product quality***

1. Table of Content.
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 Site of manufacture
      - 3.2.S.2.2 Description of manufacturing process
      - 3.2.S.2.3 Control of raw materials
      - 3.2.S.2.4 Control of critical steps and intermediates
      - 3.2.S.2.5 Process Validation
      - 3.2.S.2.6 Manufacturing Process Developments
    - 3.2.S.3 Characterization
      - 3.2.S.3.1 Elucidation of structure
      - 3.2.S.3.2 Impurities
    - 3.2.S.4 Control of drug substance
      - 3.2.S.4.1 Specifications
      - 3.2.S.4.2 Analytical Procedures
      - 3.2.S.4.3 Method Validation for Analytical Procedure
      - 3.2.S.4.4 Batch Analysis COA
      - 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 Conclusion
      - 3.2.S.7.2 Post-Approval Stability Commitment
      - 3.2.S.7.3 Stability Data
  - 3.2.P Drug Product

- 3.2.p.1 Composition
- 3.2.p.2 Pharmaceutical Development.
- 3.2.p.3 Manufacturer
  - 3.2.p.3.1 Site of Manufacture
  - 3.2.p.3.2 Batch Formula
  - 3.2.p.3.3 Description of manufacturing process
  - 3.2.p.3.4 Control of critical steps and intermediates
  - 3.2.p.3.5 Process Validation
- 3.2.p.4 Control of Excipient
  - 3.2.p.4.1 Specification of Excipient
  - 3.2.p.4.2 Analytical procedure for Excipient
  - 3.2.p.4.3 Validation for analytical procedure
  - 3.2.p.4.4 Justification of specification
  - 3.2.p.4.5 Excipients of Human or Animal Origin
  - 3.2.p.4.6 Novel Excipient
- 3.2.p.5 Control of the Product
  - 3.2.p.5.1 Specification
  - 3.2.p.5.2 Analytical Procedure
  - 3.2.p.5.3 Validation of Analytical Procedure
  - 3.2.p.5.4 Batch Analysis
  - 3.2.p.5.5 Justification of Specification
- 3.2.p.6 Reference Standards
- 3.2.p.7 Container Closure
- 3.2.p.8 Stability
- 3.2.a Appendice.
- 3.2.r Regional Information
- 3.3 Literature Reference

***Module IV: non clinical study reports***

Not required in ANDA Filing.

***Module V: clinical study reports***

1. Table of Contents.
2. Study Reports including Case Report Forms and Case Report Tabulations.



Now a days ANDA submission is not accepted in paper format. There must be eCTD format for all ANDA submissions. Size for eCTD submission is 10 GB. files ICH M2 described eCTD technical specification for submission.<sup>[7]</sup>

## CONSLUSION

The most challenging thing in the world is endorsement of the drug in USA, Europe. The USA, Europe governments giving most importance to the public health and giving top most places in their hierarchy. It is very challenging submission of dossier in these countries. The role of regulatory body is to ensure that registrant following the guidelines for developing, testing the for hat they are safe and patients well-being will be protected. Dossier is submitted in the form of CTD and ECTD format to the regulatory body. After evaluation of dossier, registrant will get approval for marketing the formulation in their territory.

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