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DOSSIER PREPARATION REQUIREMENTS FOR GENERIC DRUGS OF USA, EUROPE AND INDIA

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ABSTRACT

The main aim of the topic to review and compare the compile finished pharmaceuticals dossier for three different countries like India (CDSCO), USA (FDA) & Europe (EMA) filing process and different aspects of approval between USFDA (United States Food and Drug Administration), EMA (European Medical Agency), and DCGI (Drug Controller General of India) approval's for marketing authorization of a drug in US, EUROPE & INDIA, and their role in improving the standard laid down by them. Approval and authorization of drug product in United States, Europe & India are the most crucial ones compare to other countries in the world. Various countries have different guidelines and standard for registration and authorization of generic drugs. The primary purpose of the rules governing medicinal products in US, Europe & India is to safeguarded public health. It is the role of public regulations so that safe and effective medications reach the market.

KEYWORDS: India (CDSCO), USA (FDA) & Europe (EMA) Guidelines, Regulatory Requirements.

1. INTRODUCTION[1-4]

Common Technical Document (Dossier)

Dossier is a file document submitted for the approval of new drug or drug product. It is submitted in form of CTD. CTD is a harmonized format (template) for presenting data in the ICH regions. In some countries, it is optional. The process of reviewing & assessing dossier to support a medicinal product in view of its marketing (also called licensing, registration, approval, etc.), obviously finalized by granting of a document is called marketing

authorization. This process is performed within a legislative framework which defines the requirements necessary for application to the concerned (competent) regulatory authority, details on the assessment procedure (based on quality, efficacy and safety criteria) and the grounds for approval or rejection of the application, and also the circumstances where a marketing authorization already granted may be withdrawn, suspended or revoked.

Dossier is a file document submitted based on the requirement of regulatory agency for the approval of drug product. It is essential to submit dossier file in the form of common technical document in USA and EUROPE.

Generic drugs are approved under ANDA submission

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 Centre 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.

The European Medicines Agency (EMA) is a European agency for the evaluation of medicinal products. The EMA operates as a decentralized scientific agency of the European Union and is responsible for the protection and promotion of human and animal health, specifically through the coordination of evaluation and monitoring of centrally authorized products and national referrals, developing technical guidance and providing scientific advice. The application dossier for marketing authorization is called New Drug Application (NDA) in the USA or Marketing Authorization Application (MAA) in the European Union and other countries, or simply registration dossier.

The ICH CTD is divided into 5 modules whereas the ACTD contains of 4 parts. The reason for doing this is the fact that the ASEAN countries normally receive a reference application, which is a dossier which was already approved in other countries in the world (mostly EU and USA) and make the evaluation of the parts mainly based on the overviews and summaries.

The Module 1 of the CTD containing the regional registration and administrative information is still presented as Part 1 of the ACTD. The Module 2 of the CTD does not exist itself for the

ACTD. The Quality Overall Summary (QOS) and the overview and summaries of the nonclinical and clinical documentation (similar like the documents in ICH Module 2) are included at the beginning of these Parts. Part II of the ACTD contains the pharmaceutical-chemical-biological documentation (the quality information), which corresponds to the ICH Module 3. The nonclinical information is presented as Part III of the ACTD (equivalent to ICH Module 4) and the clinical documentation are contained in Part IV of the ACTD (to be consistent with ICH Module 5).

2. METHODOLOGY[5-10]

2.1. Marketing Authorization of Generics in Europe

European Medical Agency

EMA is the regulatory agency / decentralized body its mainly responsible in the protection and promotion of public and animal health, through the evaluation and supervision of medicines for human and veterinary use. The EU has one of the most highly regarded regulatory systems in the world.

EU consists of 27 member states

Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxemburg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom and three countries which are member of European Free Trade Agreement (EFTA) Iceland, Norway, and Liechtenstein.

EUROPEAN FILING PROCEDURE

EU establishes 4 different drug approval processes

- Centralized Procedure
- Decentralization Procedure
- National Procedure
- Mutual Recognition Procedure
- All medicines must be authorized before they can be marketed and made available to patients.
- In Europe Union (EU), there are two main routes for authorized medicines:

- A centralized route
- A national route.

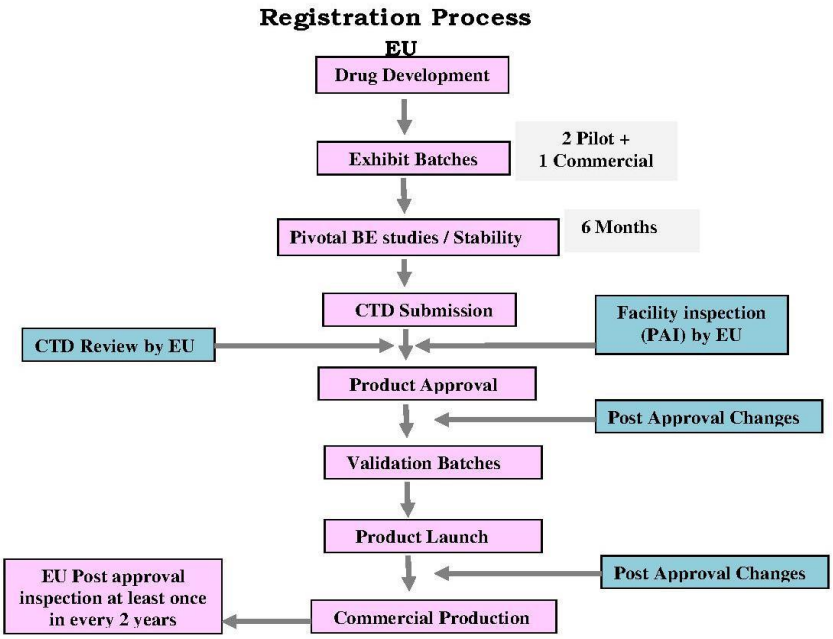

Fig 1: Generic drugs Filling and Registration process in Europe.

2.2. USFDA: (UNITED STATES FOOD AND DRUG ADMINISTRATION)

It is the regulatory agency which is responsible for safety regulation of the food and drug products in US.

The United States of America & Europe are the two main regulatory agencies in the world US is a single country but EU is a union of countries.

United States is the world's most stringent standards for approving new drugs.

Drug approval standards in the United States are considered by many to be the most demanding in the world.

FILING PROCEDURES IN UNITED STATES

Investigational New Drug Application (IND)

It is an application file to the FDA in order to start clinical trials in humans on the basis of the data obtained from the preclinical trials.

New Drug Application (NDA)

If clinical studies confirmed that new drug is relevantly safety and effective will not pose risk to patients, the manufacturer file a New Drug Application (NDA) in the United states.

Abbreviated New Drug Application (ANDA)

It's an application made for approval of Generic Drugs. The sponsor is not required to reproduce the clinical studies that were done for the original, brand name product.

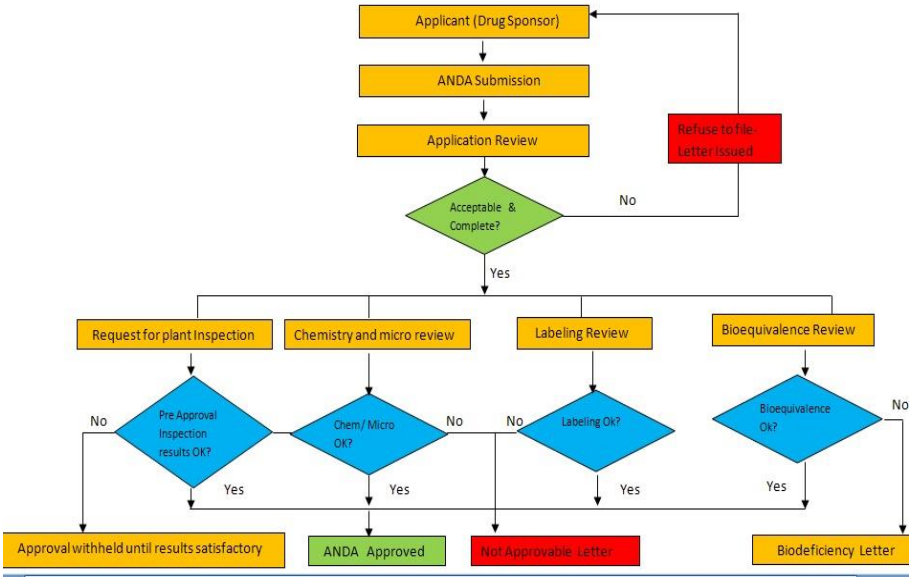

Fig 2: Review by FDA And Procedure Involved in Reviewing.

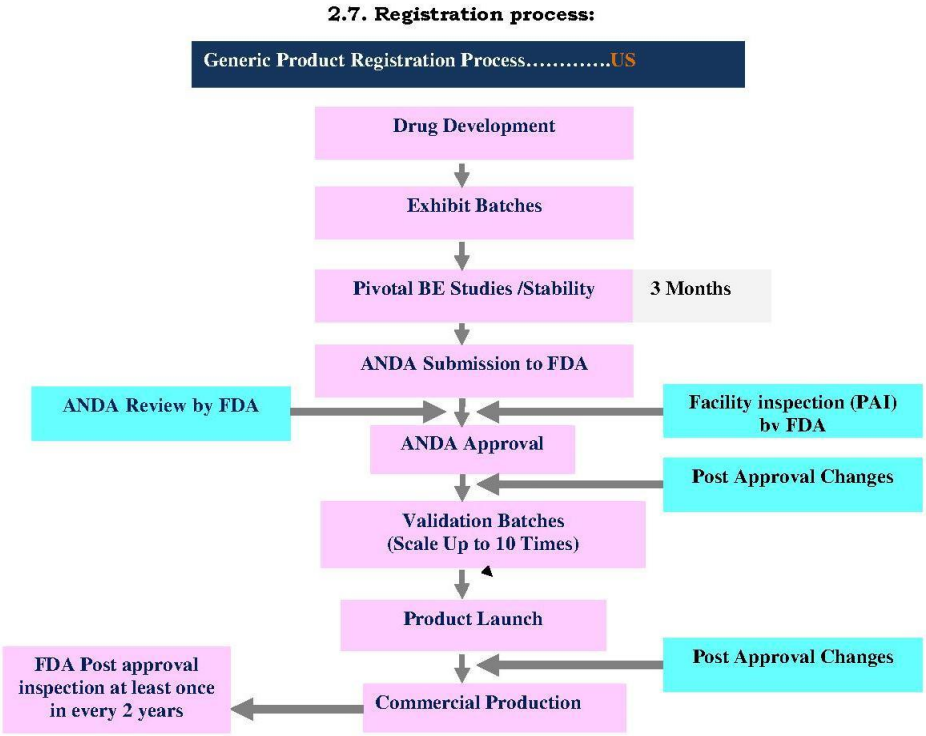

Fig-3: Drugs Filing Registration process in US.

2.3. REGULATORY GUIDELINES FOR DOSSIER SUBMISSION IN INDIA

India is primarily a branded generic market. India did not follow any patent protection laws up to 2005 generic drugs sold by both big pharma companies (generic copies of the innovator's molecules 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.

CDSCO

A licensing authority for approval of new dug proposed to be imported.

Head office located in New Delhi & functioning under the control of directorate general of Health services, MHFW, Govt of India.

DCGI

It is Responsible for approval of new drugs & Clinical trails to be conducted in India Appointed by Central Govt of India.

Process of Filing as per CTD.

The filing of a dossier in CTD format compulsory in India (or) The CTD is only a format for submission of information to CDSCO.

CTD

The Common Technical Documents (CTD) is a set of specification for application dossier for the registration of Medicines and designed to be used across Europe, India, United States and the Japan.

It is an internationally agreed format for the preparation of application regarding new drugs intended to be submitted to regional regulatory authorities in participating countries.

CTD is maintained by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH).[4]

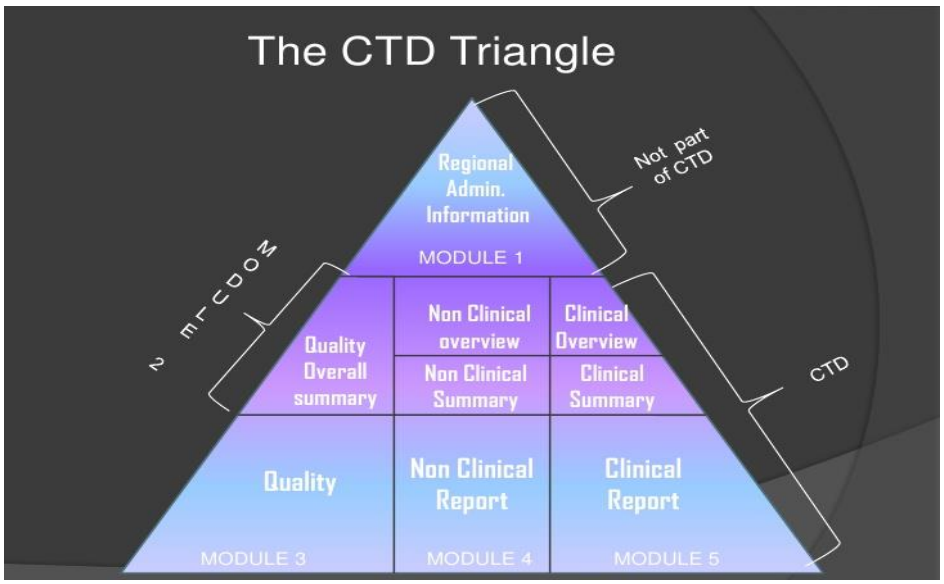

Fig 4: CTD Module.

3. REGULATORY DIFFERENCES BETWEEN USFDA, EMA AND CDSCO[10-13]

Table 1: Principle differences between US, EU & INDIA

Requirements	US	EU	INDIA
Agency	One Agency USFDA	Multiple Agencies • EMEA • CHMP • National Health Agencies	One Agency DCGI
Registration Process	One Registration Process	Multiple Registration Process • Centralized (European Community) • Decentralized (At least 2 member states) • Mutual Recognition (At least 2 member states) • National (1 member state)	One Registration Process
TSE/BSE Study data	TSE/BSE Study data not required	TSE/BSE Study data required	TSE/BSE Study data required
Braille code	Braille code is not required on labelling	Braille code is required on labelling	Braille code is not required on labelling
Post-approval changes	Post-approval changes in the approved drug: • Minor changes • Moderate changes • Major changes	Post-variation in the approved drug: • Type IA Variation • Type IB Variation • Type II Variation	Post approval changes: Major quality changes Moderate quality changes

Table 2: Administrative Requirements

Requirements	US	EU	INDIA
Application	ANDA / NDA	MAA	MAA
Debarment classification	Required	Not Required	Not Required
Number of copies	3	1	1
Approval Timeline	~18 Months	~12 Months	12 - 18 Months
Fees	Under $2 million-NDA Application $51,520 – ANDA Application	National fee (including hybrid applications): £103,059 Decentralised procedure where UK is CMS: £99,507	50,000 INR
Presentation	eCTD & Paper	eCTD	Paper

Table 3: Finished Product Control Requirements

Requirements	US	EU	INDIA
Justification	ICH Q6A	ICH Q6A	ICH Q6A
Assay	90 - 100 %	95 - 105 %	90 - 110 %
Disintegration	Not Required	Required	Required
Colour Identification	Not Required	Required	Required
Water Content	Required	Not Required	Required

Table 4: Manufacturing & Control Requirements

Requirements	US	EU	INDIA
Number of batches	1	3	1
Packaging	A minimum of 1,00,000 Units	Not Required	Not addressed
Process Validation	Not required at the time of submission	Required	Required
Batch Size	1 pilot scale or minimum of 1 lakh units whichever is higher.	2 pilot scale plus 1 lab batch or minimum of 1 lakh units whichever is higher.	Pilot scale batch

Table 5: Stability Requirements

Requirements	US	EU	INDIA
Number of batches	3 Pilot Batch or 2 Pilot Batch & 1 Small scale	2 Pilot Scale (If API Stable) 3 Primary Batches (If API unstable)	2 Pilot Scale/Production scale(If API Stable) 3 Primary Batches (If API unstable)
Condition: Long term stability, Accelerated stability,	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months); Intermediate: 30°C/65%RH	Long term: 25°C/60%RH Accelerated: 40°C/75%RH(0,3,6 months) Intermediate: 30°C/65%RH	Long term: 30°C/70%RH Accelerated:40°C/75%RH (0,3,6 months)
Minimum time period at Submission	6 Months Accelerate & 6 Months long term	6 Months Accelerate & 6 Months long term	6 Months Accelerate & 6 Months long term
Container orientation	Inverted & Upright	Do not address	upright and inverted
Clause	21 CFR part 210 & 211	Volume 4 EU Guidelines for medicinal products	ICH Q1F
QP Certification	Not Required	Required	Required

Table 6: Bioequivalence Requirements

Requirements	US	EU	INDIA
CRO (Audits)	Audited by FDA	Audited by MHRA	CDSCO
Reserve Sample	5 times the sample required for analysis	No such requirement	-
Fasted / Fed	Must be as per OGD recommendation	No such requirement	As CDSCO recommendation
Retention of samples	5 years from date of filing the application	No such requirement	3 years from date of filing the application
BE study for generic drugs	Against US RLD in any country. To refer 'BE recommendations' in FDA site for guidance.	Against EU reference product (ERP) in any country	Against US/EU/Australia RLD in any country except Thailand, where BE to be done locally against local reference product.

4. CONCLUSION

Approval and authorization of drug product in United States, Europe & India are the most crucial ones compare to other countries in the world. Various countries have different guidelines and standard for registration and authorization of generic drugs. The primary purpose of the rules governing medicinal products in US, Europe & India is to safeguarded public health. It is the role of public regulations so that safe and effective medications reach the market. Thus the above work helps the applicants in assisting them for the procedure to be followed for marketing authorization since many regulatory authorities are involved. It also provides a brief procedure of steps involved in applying an application to till its approval by the authorities and the common format of filing them. From the detailed study conducted in different guidelines, could able to provide a single document giving brief information to obtain generic dossier approval from CDSCO, EMA and USFDA. The project summaries the various and specific requirements as per the specific countries guidelines to facilitate the new entrant will get benefited without going through the consultants at the start up stage.

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