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Comparison of Drug Approval Process in United States & Europe

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Abstract:

This topic aims at reviewing the drug filing and different aspects of obtaining United States Food & Drug Administration (USFDA) and European Medicines Agency (EMA) approval for a drug in order to get a Marketing Authorization in US & Europe and their effective role in improving the standards laid down by them. All new / generic drug products must be approved by the respective regulatory agency governing the respective market before a particular product can be introduced into the market. By law, all new drugs must first be shown to be safe and effective before they can be approved by the respective regulatory agency for marketing. USFDA is the regulatory agency which is responsible for safety regulation of the food and drug products in US. EMA is the regulatory agency/ decentralized body which is responsible for safety regulation of the food and drug products in Europe. Drug approval process in USFDA involves submitting of an Investigational New Drug Application, followed by submission of New Drug Application. The applications are reviewed and agency officials examine the drug's safety and efficacy data and the drug is approved. EU establishes 4 different drug approval processes:

1) Centralized Procedure
2) Decentralized Procedure
3) National Procedure
4) Mutual Recognition Procedure

***Keywords*:** Drug Approval, EMA, USFDA

INTRODUCTION:

The United States of America & Europe are the two main regulatory agencies in the world apart from Japan. US is a single country but EU is a union of countries. Therefore the Drug approval process in both the regulatory agencies has been summarized for easy understanding.[1] The basic regulation can be understood from Fig 1.

Drug Approval in United States:-

The United States has perhaps 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.[1-3]

Investigational New Drug (IND) Application

It's an application filed to the FDA in order to start clinical trials in humans if the drug was found to be safe from the reports of Preclinical trials. A firm or institution, called a Sponsor, is responsible for submitting the IND application.[4] A pre - IND meeting can be arranged with the FDA to discuss a number of issues:

- The design of animal research, which is required to lend support to the clinical studies
- The intended protocol for conducting the clinical trial
- The chemistry, manufacturing, and control of the investigational drug

Such a meeting will help the Sponsor to organize animal research, gather data, and design the clinical protocol based on suggestions by the FDA. A clear flowchart of the IND process is illustrated in figure 2.

New Drug Application (NDA)

If clinical studies confirm that a new drug is relatively safe and effective, and will not pose unreasonable risks to patients, the manufacturer files a New Drug Application (NDA), the actual request to manufacture and sell the drug in the United States.[5, 6] The process of NDA has been illustrated in figure 3.

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. Instead, generic drug manufacturers must demonstrate that their product is the same as, and bioequivalent to, a previously approved brand name product.[7] The process of ANDA has been illustrated in figure 4.

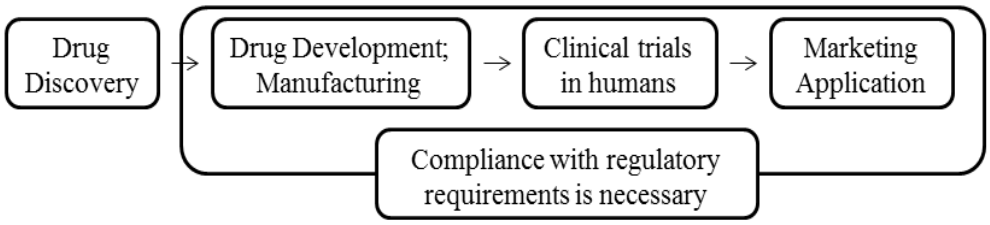


Figure 1: The Basic Regulation

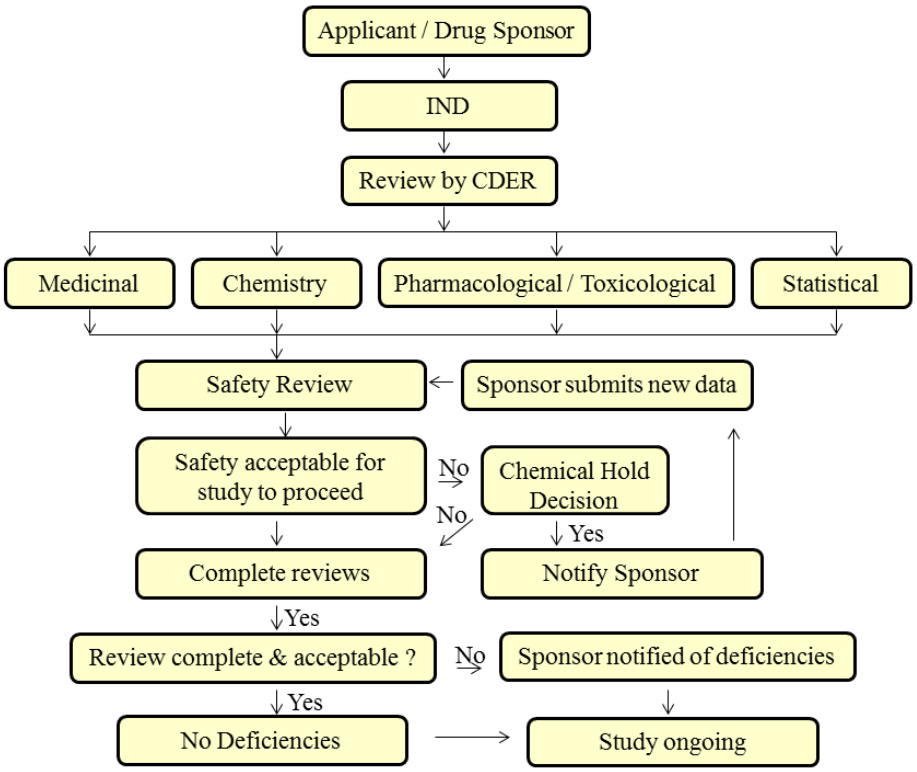


Figure 2: Investigational New Drug Application

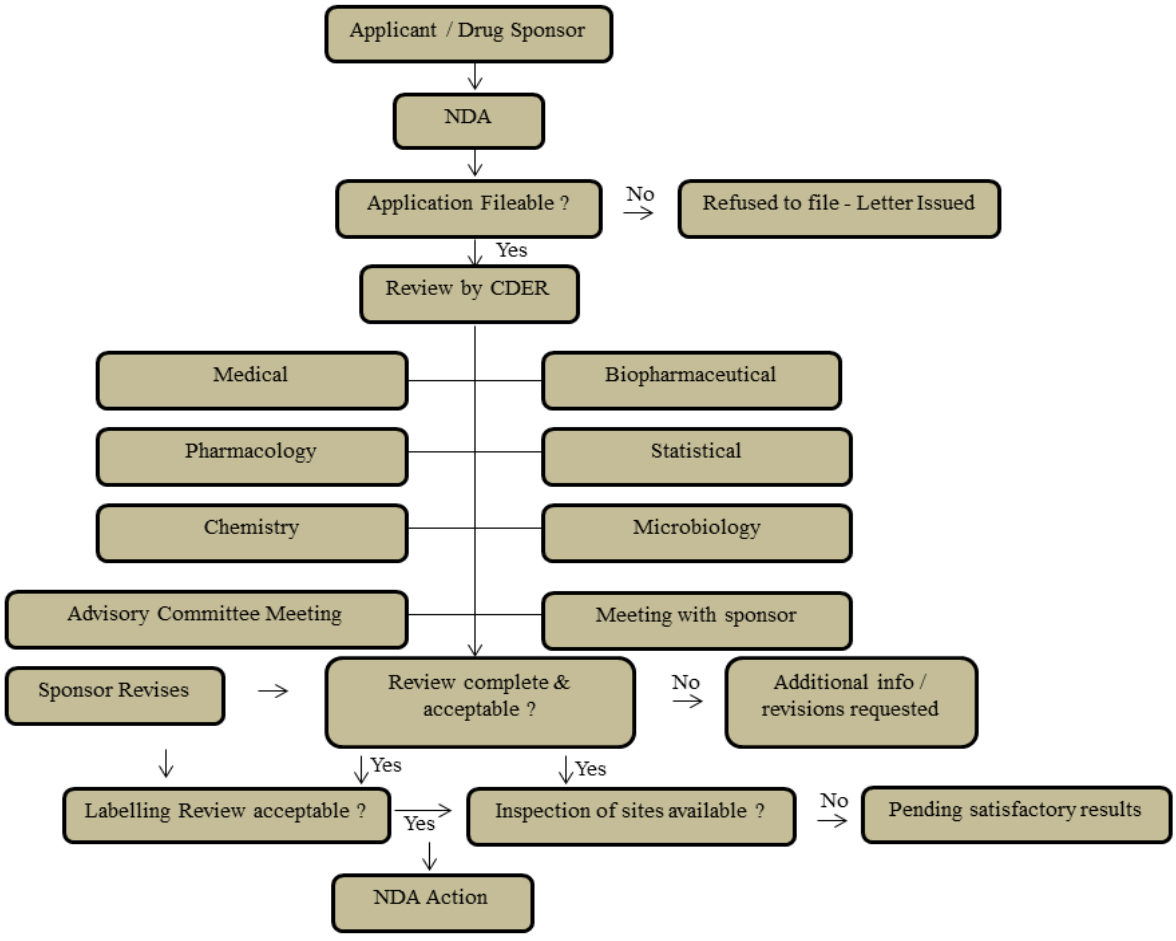
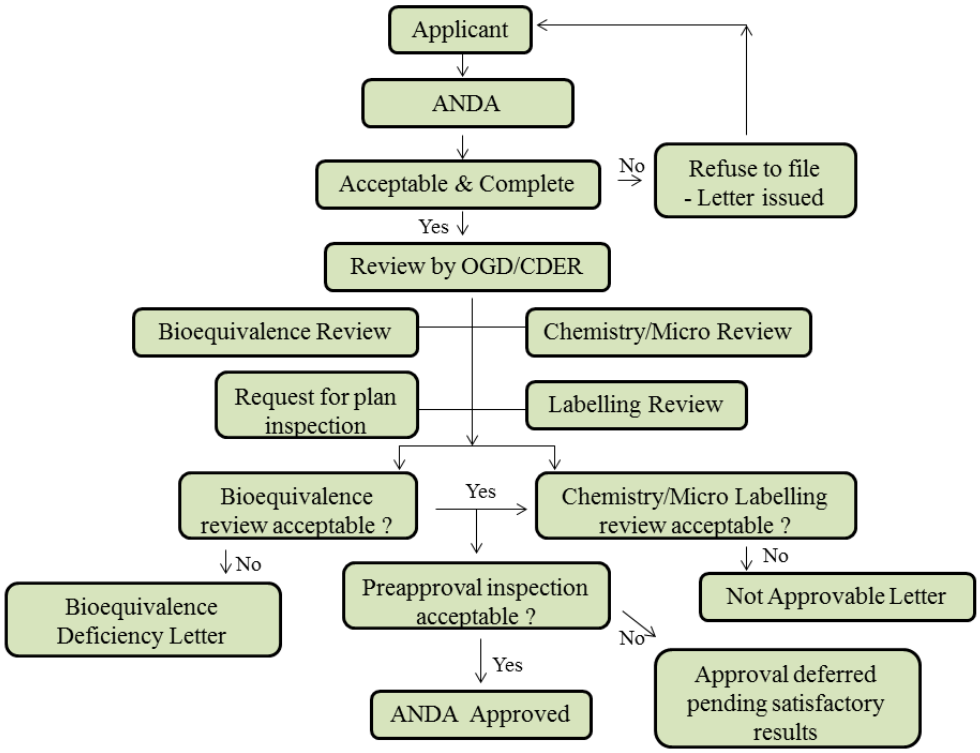


Figure 3: New Drug Application



Generic Drugs Approval (ANDA Approval)

Figure 4: Abbreviated New Drug Application (for Generic Drugs)

Drug Approval in Europe:-

Similar to the US requirements, there are two regulatory steps to go through before a drug is approved to be marketed in the European Union. These two steps are clinical trial application and marketing authorization application. There are 27 member states in the European Union (as of August 2007); Clinical Trial Applications are approved at the member state level, whereas marketing authorization applications are approved at both the member state or centralized levels.[8]

Centralized procedure

The centralized procedure is one which allows applicants to obtain a marketing authorization that is valid throughout the EU.[9]

- 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:

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

Mutual Recognition Procedure

The Mutual Recognition procedure allows applicants to obtain a marketing authorization in the member states (Concerned Member State) other than the member state (Reference Member State) where the drug is previously approved.[10]

- 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.
- *Nationalized Procedure*

The Nationalized procedure is one which allows applicants to obtain a marketing authorization in one member state only.[11,12]

- In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.
- New active substances which are not mandatory under Centralized procedure can obtain marketing authorization under this procedure.
- Timeline for this procedure is 210 Days.

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.[13,14]

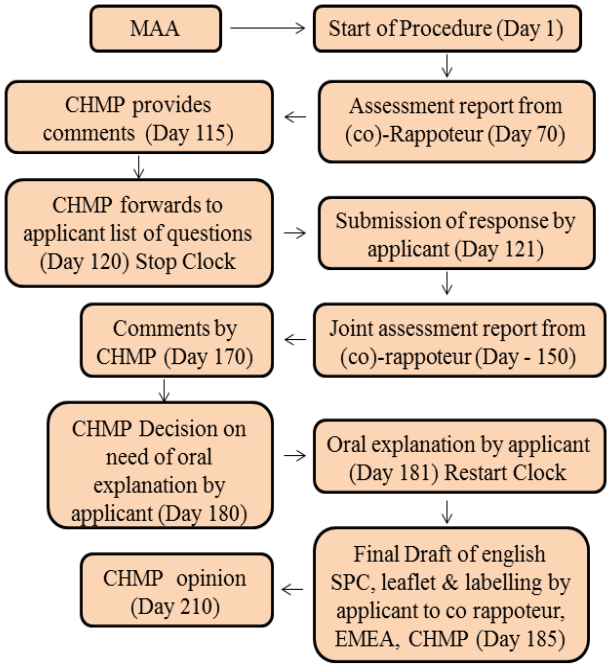


Figure 5: Centralized Procedure

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.
- Time: 210 days.

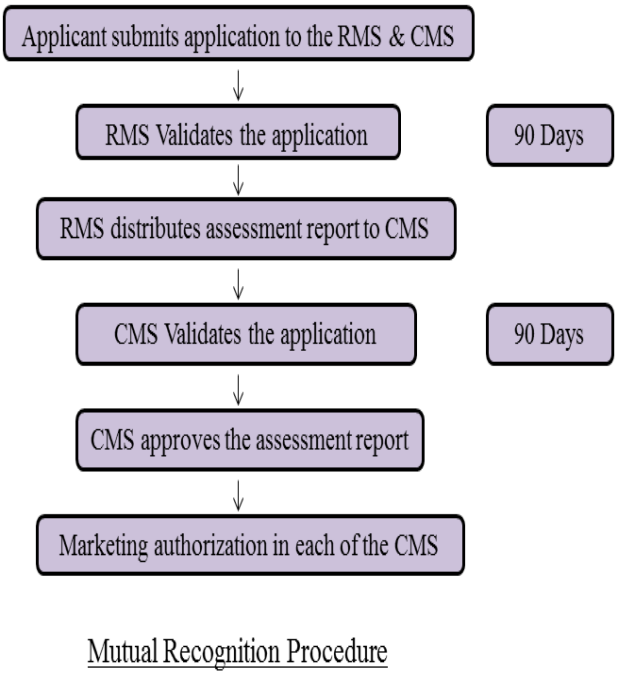


Figure 6: Mutual Recognition Procedure

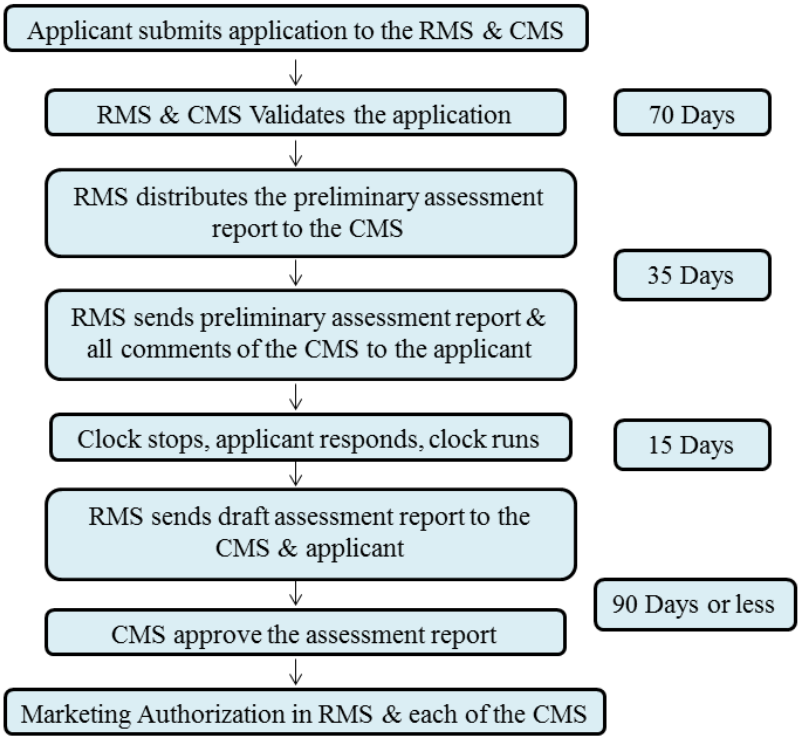


Figure 7: Decentralized Procedure

RESULTS & DISCUSSION:

A Brief comparison is done for both the regulatory agencies is done for clear understanding in Table 1

Comparative study of Dossier submission of a drug product

Administrative

This involves the administrative requirements like application, number of copies, fees and type of presentation required mentioned in Table 2

Finished Product Control

The requirements are clearly stated in Table 3

Manufacturing & Control

The requirements are clearly stated in Table 4

Stability

The requirements are clearly stated in Table 5

Bioequivalence

The requirements are clearly stated in Table 6

World Pharma Market

The World Pharma market share is depictive in the Figure 8

Table 1: Principle differences between USFDA & EU

USFDA	EU
➢ One Agency	➢ Multiple Agencies ▪ EMEA ▪ CHMP ▪ National Health Agencies
➢ One Registration Process	➢ Multiple Registration Process ▪ Centralized -(European Community) ▪ Decentralized - (Atleast 2 member states) ▪ Mutual Recognition - (Atleast 2 member states) ▪ National - (1 member state)
➢ TSE / BSE Study data not required	➢ TSE / BSE Study data required
➢ Braille code is not required on labelling	➢ Braille code is required on labelling
➢ The changes in the approved drug can be done by filing ▪ PAS ▪ CBE - 30 / CBE ▪ Annual Report	➢ The changes in the approved drug can be done by filing ▪ Type IA Variation ▪ Type IB Variation ▪ Type II Variation

Table 2: Administrative Requirements

S. No	Requirement	USFDA	EU
1	Application	ANDA / NDA	MAA
2	Debarment classification	Required	Not Required
3	Number of copies	3	1
4	Approval Timeline	18 Months	12 Months
5	Fees	No fees	10 - 20 Lakh
6	Presentation	eCTD& Paper	eCTD

Table 3: Finished Product Control Requirements

S. No	Requirement	USFDA	EU
1	Justification	ICH Q6A	ICH Q6A
2	Assay	90 - 100 %	95 - 105%
3	Disintegration	Not Required	Required
4	Color Identification	Not Required	Required
5	Water Content	Required	Not Required

Table 4: Manufacturing & Control Requirements

S. No	Requirement	USFDA	EU
1	Number of batches	1	3
2	Packaging	A minimum of 1,00,000 Units	Not Required
3	Process Validation	Not required at the time of submission	Required
4	Batch Size	Minimum of 1,00,000 Units	Minimum of 1,00,000 Units

Table 5: Stability Requirements

S. No	Requirement	USFDA	EU
1	Number of batches	1	2
2	Condition	25/60 - 40/75	25/60 - 40/75
3	Date & Time of Submission	3 Months Accelerate & 3 Months long term	6 Months Accelerate & 6 Months long term
4	Container orientation	Inverted & Upright	Do not address
5	Clause	21 CFR part 210 & 211	Vol 4 EU Guidelines for medicinal products
6	QP Certification	Not Required	Required

Table 6: Bioequivalence Requirements

S. No	Requirement	USFDA	EU
1	CRO	Audited by FDA	Audited by MHRA
2	Reserve Sample	5 times the sample required for analysis	No such requirement
3	Fasted / Fed	Must be as per OGD recommendation	No such requirement
4	Retention of samples	5 years from date of filing the application	No such requirement

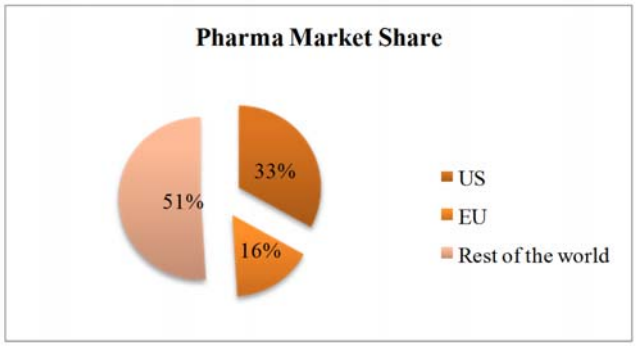


Figure 8: Pharma Market Share

CONCLUSION:

The Drug approvals in the United States & Europe are the most demanding in the world. The primary purpose of the rules governing medicinal products in US & Europe is to safeguard public health. It is the role of public regulatory authorities to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trialed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

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