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Review Article

**COMPARATIVE STUDY OF NEW DRUG APPLICATION
PROCEDURE IN US, EU AND INDIA****Kahrgawe Lakshmi*, Shaik Zareena Begum**Department Of Regulatory Affairs, Princeton College Of Pharmacy, Pocharam, Hyderabad,
Telangana 500088.**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.**Corresponding author:****Kahrgawe Lakshmi,**Department of Regulatory Affairs, Princeton college of Pharmacy,
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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.

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.

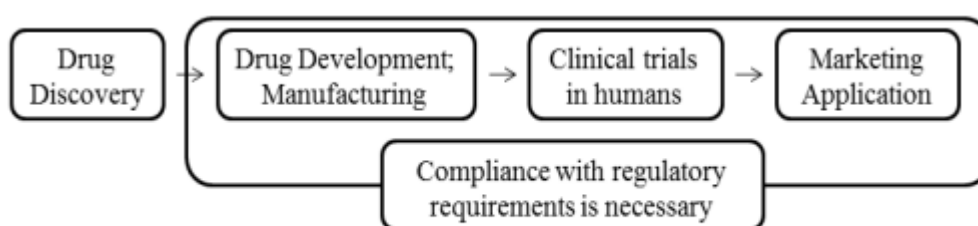
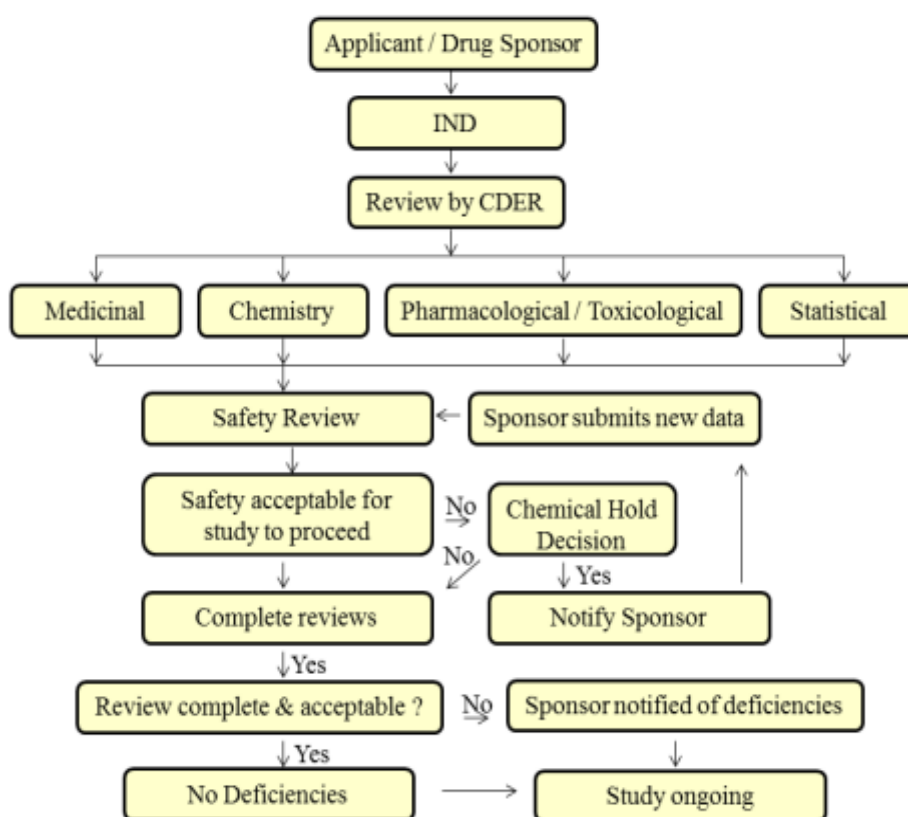


Figure 1: The Basic Regulation



Investigational New Drug Application (IND)

Figure 2: Investigational New Drug Application

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.

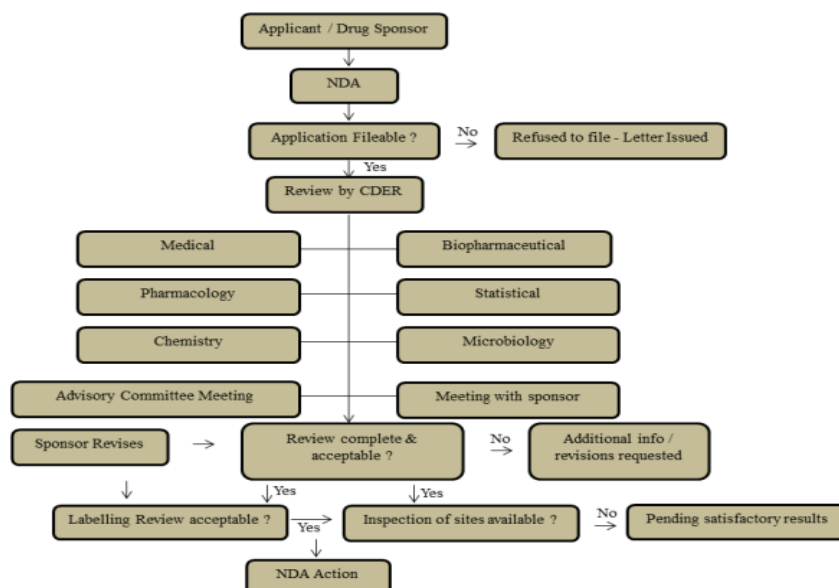
**New Drug Application (NDA)**

Figure 3: New Drug Application

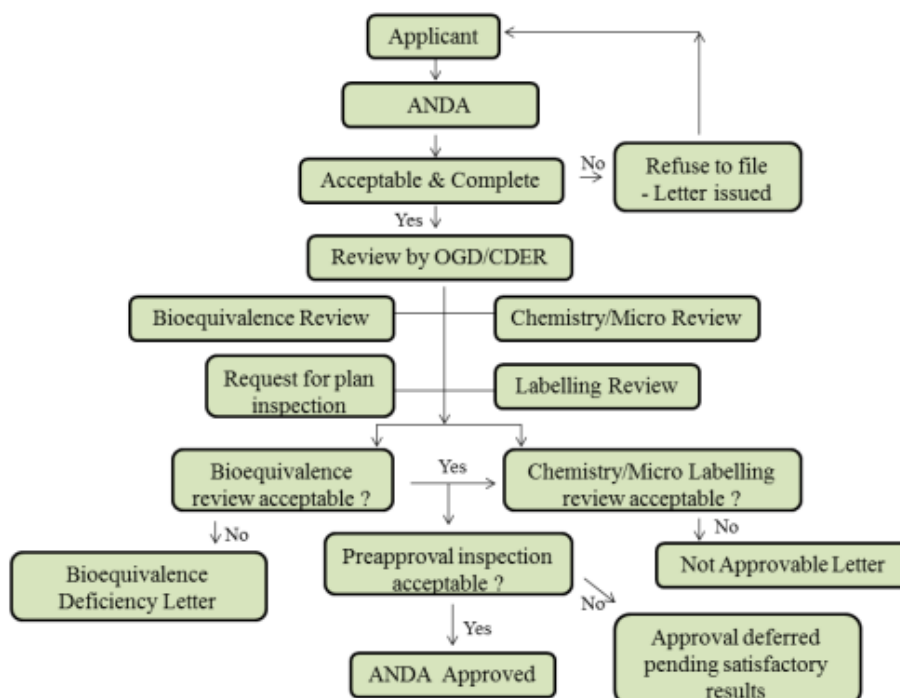
**Generic Drugs Approval (ANDA Approval)**

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]

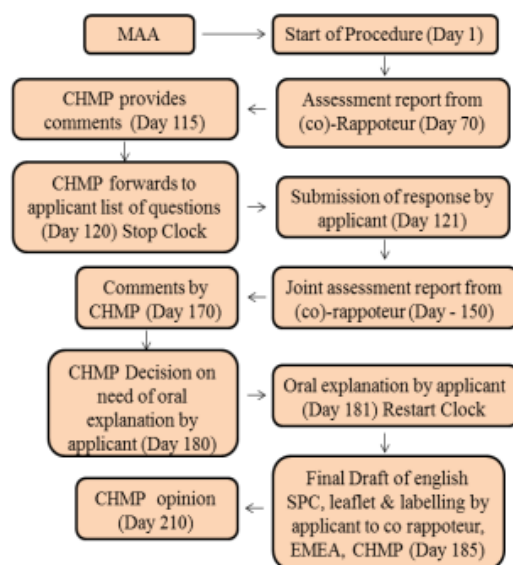
- ♣ In order to obtain a national marketing authorization, an application must be submitted to the competent authority of the Member State.

- ♣ 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]

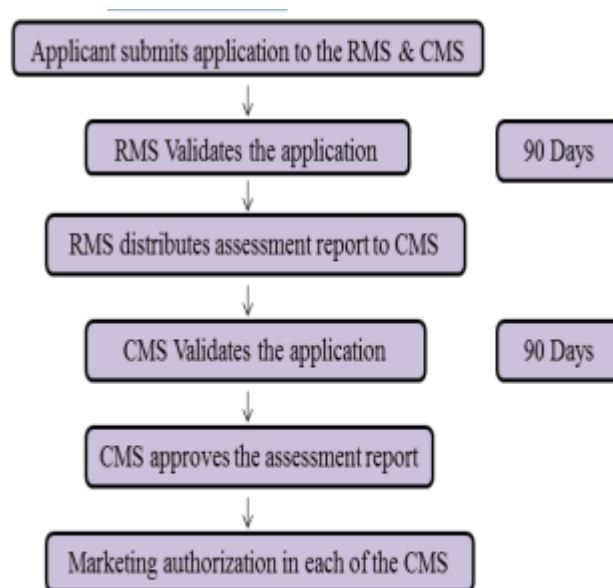


Centralized Procedure

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.



Mutual Recognition Procedure

Figure 6: Mutual Recognition Procedure

The advent of 1950s and 1960s saw tremendous technological advances thereby giving a fillip to innovation in the field of Pharmaceutical and Medical Device Industry. Today these Industries are estimated to worth billions of dollars. Medical Devices have enhanced the quality of healthcare at our disposal by making diagnosis, prevention and treatment of diseases and serious health conditions, easier and efficient. It is worth mentioning that development of Medical Devices, vis-a-vis, Pharmaceuticals is less expensive and time consuming. The GMP requirements are by far less stringent than Pharmaceuticals.

However, with passage of time, enhanced technology has become increasingly complicated and intricate, so much so, that it has several times circumvented the understanding of Medical Professionals, Device developers and Regulators. These parties often encounter problems in understanding deficiencies and gaps in the development process consequently resulting in Patient injuries, adverse events (serious or non-serious) and even deaths, and leaving room for Public Hazard. Thus it is clear that there is a need for effective regulation to be put on devices being circulated in the International and National commerce.

The Regulations of Medical Devices is vast and rapidly evolving field that is often complicated by

legal and technical issues, for instance information on patent status, market approvals in other regions as a legal requirement, safety and efficacy data, engineering aspects etc. for technical requirements. Various Regional Regulatory Authorities (RRAs) have come up with regulations from time to time. The USFDA put regulations in place in 1976, through Medical Device Amendment in the Food, Drugs and Cosmetic Act of 1938.

The European Commission, of EU regulates Medical Devices through Medical Device Directive, 93/42/EEC of 1993. The Member states follow the directives of EU with modifications as per pertinent rules and obligations.

The CDSCO, Government of India, regulates a handful of devices under Central License Approval Authority scheme (CLAA), called Notified Devices. Government of India is mulling changes to extant regulatory apparatus.

Current Global Trends in Medical Device Industry

The global market for medical devices is estimated over \$ 220 billion for the year 2015. The United States of America, with about 45% market share is the dominant market for medical devices followed by European market share of 30% and Japan with share of 10% and other 15% includes markets of Asia Pacific and Latin America (Figure 7).

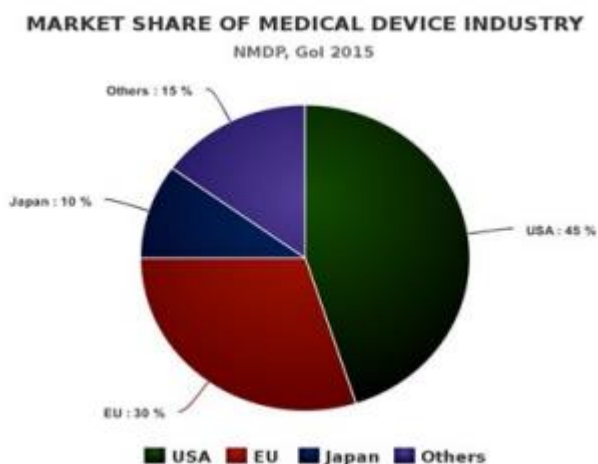


Fig 7: Market Share Of Medical Device Industry

Medical devices sector in India is relatively small as compared to the rest of the manufacturing industry, though India is one of the top twenty markets for medical devices in the world and is 4th largest market in Asia after Japan, China and South

Korea. Although accurate data and figures are not available on the subject, an educated guess would place the sector at about Rs. 30,900 crores in production terms¹⁵⁻²⁰. Medical Device Industry in India is predominantly import driven accounting for over 65% of the total market (Figure 8).

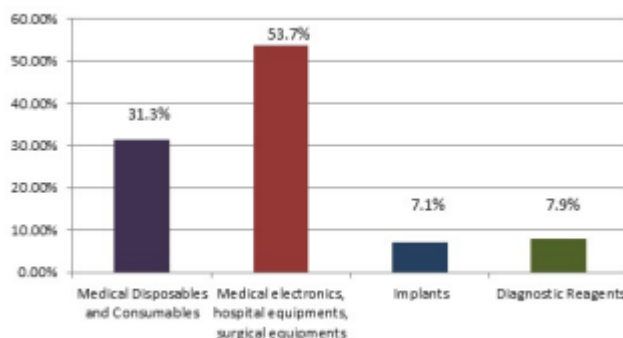


Fig 8 : Components Of Indian Medical Device Industry

Some of the top medical devices companies by revenue (in no particular order), 2017, in India include²¹:

- Johnson & Johnson.
- General Electric Co.
- Medtronic Inc.
- Siemens AG.
- Baxter International Inc.

PROCEDURE OF MARKETING AUTHORIZATION IN THE UNITED STATES OF AMERICA

In the United States of America, Medical Devices are regulated by Food and Drug Administration (FDA). FDA's Centre for Devices and Radiological Health (CDRH) is responsible for regulating arms who manufacture, repackage, re-label, and/or import medical devices sold in the United States.

A system of Device classification is followed in the US. Devices are classified into Class I, II or III. Each device is assigned to a panel (Cardiovascular,

Anaesthesiology etc.). The panel determines the Class and special controls and exemptions applicable to the device.

General Controls include:

- Establishment Registration by manufacturers, distributors, repackagers and re-labellers,
- Medical Device Listing with FDA of devices to be marketed,
- Manufacturing the devices in accordance with Good Manufacturing Practices,
- Labelling medical devices in accordance with the labelling regulations, 21 CFR 801 or 21 CFR 809,
- Medical Device Reporting of adverse events as identified by the user, manufacturer and/or distributor of the medical device.

Special Controls may include:

- Adherence to performance standards, guidance documents,
- Implementation of post-marketing surveillance measures,
- Special labelling.

The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. The Devices are placed in Class I, II or III. All the classified devices are available on the website of FDA.

Class I devices are deemed as non-life sustaining and present minimal harm potential to user. These devices are typically simple in design, manufacture and have a history of safe use. Their failure poses no risk to life and hence are subject to general control and require least regulations, these devices have to comply with Quality System Regulations (QSR) laid in 21 CFR Part 820 and labelled according to 21 CFR Part 821. Although most are exempt from 510 (k) pathway and some are even exempt from QSR. For example tongue depressors are exempt from 510 (k) but stethoscopes are not.

Class II medical devices are devices where General Controls are not sufficient to assure safety and effectiveness and existing methods/standards/guidance documents are available to provide assurances of safety and effectiveness. In addition to compliance with General Controls, Class II devices are required to comply with Special Controls.

Special Controls may include:

- Special labelling requirements,
- Mandatory performance standards, both International and United States,
- Post-marketing surveillance,
- FDA medical device specific guidance.

Information on Class II exempt devices is located within the device regulation, 21 CFR 862 through 892. Devices falling in these class are cleared for sale only through 510 (k) regulatory pathway, where the applicant demonstrates that the 'Device' is substantially equivalent to an existing device called, 'Predicate device' and Clinical Trials may be required for devices falling in this class. The information required in a 510 (k) submission is denied 21 CFR 807.87.

Class III devices usually support or sustain human life, are of substantial importance in preventing impairment of human health, or present a potential unreasonable risk of illness or injury to the patient. Devices falling in this class have to demonstrate safety and efficacy through Clinical Trials.

For Class III medical devices, sufficient information is not available to assure safety and

effectiveness through the application of General Controls and Special Controls. Typically a Pre-Market Approval (PMA) submission to the FDA is required to allow marketing of a Class III medical device. Section 515 (c) (1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) species the required contents of a PMA.

Some devices falling in Class III includes replacement heart valves, PTCA balloons, implanted cerebella stimulators, Pacemaker. These devices mandatorily require Phase IV trials data. A few Class III medical devices are required to only have a 510 (k) cleared by the FDA to be marketed. Manufacturers are required to submit their application for review. Depending on the complexity of the new or modified medical device, the FDA Review of a 510 (k) submission takes between 20 and 90+ days. The more complex the changes or comparison required to support the safety and effectiveness of the new or modified medical device, the longer the FDA review process. The FDA has a statutory 180-day review cycle for PMA applications. Often PMA applications require medical advisory board review prior to the FDA granting approval to market the medical device. A facility inspection verifying the manufacturing systems present to manufacture the medical device is usually performed prior to FDA PMA approval. FDA approval of a PMA often requires significantly more than 180 days ²².

The FDA reviews the application (510 (k) or PMA) and if satisfied with, data posts online a 510 (k) clearance letter or PMA Approval Letter. Following which a device could be marketed in the USA. Any changes to constitution of device shall be informed to FDA through supplement filing as per the prescribed timelines.

Steps for marketing approval in USA

1. Classify Medical Device.
2. Implement Quality Management System (GMP Requirements).
3. Submission of Clinical Trial data, If Applicable (Investigational Device Exemption (IDE)).
4. Submission of Marketing Approval Application (510 (k) Premarket Notification Premarket Approval Application).
5. FDA 510 (k) Clearance Letter or PMA Approval Letter.
6. FDA Quality system inspection of Manufacturing Facility.
7. Medical Device Listing in FURLS System.
8. Establishment Registration in FURLS System (Figure 9).

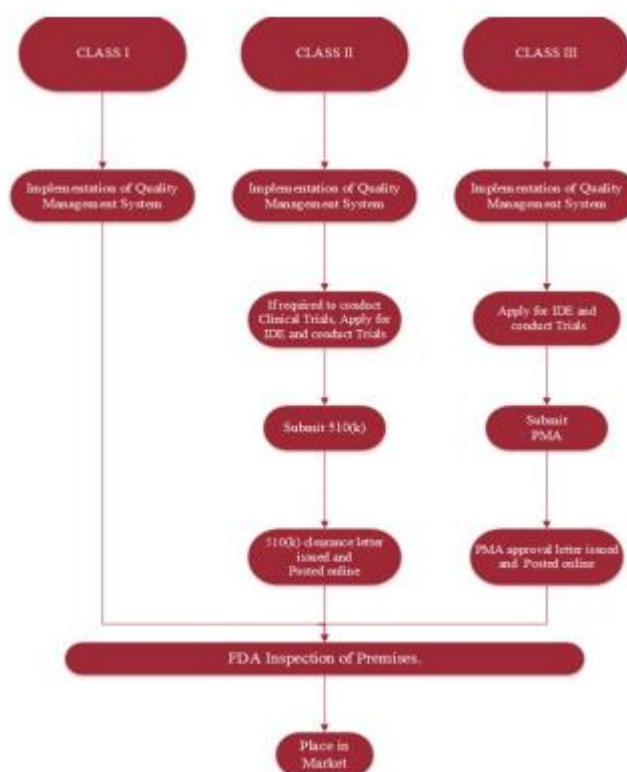


Fig9 : Regulatory Approval Pathways In USA

Procedure of Marketing Authorization in European Union

In EU, there is decentralized procedure of marketing authorization as no single body regulates Medical devices. A system of third party compliance is followed. Notified Bodies are the third party that issue Quality Assurance certificates and ensures post approval compliance to Quality Management System (QMS).

Medical Devices are regulated by Medical Devices Directive, which consists of three directives that regulate the safety and marketing of medical devices in Europe. The three directives are:

- Medical Device Directive (MDD 93/42/EEC),
- Active Implantable Medical Device Directive (AIMDD 90/42/EE),
- In vitro Diagnostic Medical Device Directive (IVDMDD 98/79/EC).

These directives are regularly updated. The directive 93/42/EEC has been thus far, amended five times. The last amendment was 2007/47/EC, which came into effect in March 2010.

A system of product classification is followed in EU, whereby Medical Devices are classified into classes I, IIa, IIb and III, depending upon the risk involved with usage of device. The criteria for class determination are laid in Annex IX of MDD 93/42/EEC. These criteria take into account the following:

- Duration of contact,
- Invasiveness of device,
- Source of Energy of device,

- Active Principle of Device, if used in combination, as for Drug Eluting Coronary Stents. Some examples of devices and their class are:
Class I: Blood Pressure Cuff; Hospital Bed;
Class IIa: Hearing aid, X ray diagnostic equipment;
Class IIb: Ventilator, Blood bags;
Class III: PTCA balloon, Drug Eluting Coronary Stent.

It is worth mentioning that all devices all devices which are of human blood derivative and or utilizing animal tissues or derivative fall in Class III.

All devices used for contraception or the prevention of transmission of Sexually Transmitted Diseases are in class IIb, unless implantable for long term invasive devices which fall in Class III. Medical devices intended for recording of X-ray diagnostic images are in Class IIa.

Medical Devices cannot be placed on European Market without conforming to the strict safety requirements of EU. A device must bear CE mark, except for Custom-made devices; Devices for clinical investigation, health protection-urgent unusual circumstances; humanitarian use and In-house use.

Devices are labelled as per Annex I of Council Directive 93/42/EEC in national language and use of appropriate symbols is recommended. Conformity assessment of the Device is performed by a Notified Body.

Technical Documentation should be submitted to the NB for assessment. Documents are accepted in IMDRF format (STED) or as per Notified Bodies

Medical Devices (NB-MED) recommend document (NB-MED/2.5.1/Rec 5) 'Technical documentation'. STED and NB-MED format include comprehensive information on device.

The Notified Body is effectively responsible for pre-market evaluation of medical devices. They monitor all aspects of the evaluation from manufacturing process to post-market surveillance. They review all data (including clinical data), conduct regular inspections (including impromptu on-site inspections) and collect reports regarding safety. Adverse event reporting to the Competent Authority is mandatory for the manufacturer. Once a device is reviewed and deemed acceptable, it receives the CE marking ²³.

Once NB clears a device, manufacturer can declare conformity and place the device in market. An NB can conduct surprise audit to ensure conformance to QMS by the Manufacturer. Documents must be kept at disposal of Competent Authority for five years

(fifteen Years for implantable Devices).

The timelines for gaining approval differs for different class of devices, complexity of design and risk to the user with use of device. Since being approved for marketing class I devices' validity is indefinite and for Class II and III devices validity is for 3 years.

Any change in the constitution of device, the manufacturer has to be informed to the Notified Body as per prescribed timelines.

Procedure of Marketing Authorization in India

The Government of India regulates medical devices through a specialized division called, Medical Device and Diagnostics Division, CDSCO, Ministry of Health and Family Welfare. Only a few Medical Devices and Diagnostic kits, called Notified Devices, are regulated under Central Licensing Approval Authority (CLAA) scheme for the purpose of Manufacture, Import, Sale and Distribution. Drug Controller General of India (DCGI) is the Central Licensing Authority.

The regulation of Notified Medical Devices is overseen by both, the central government and the state governments. Under the applicable regulatory framework, the functions of manufacture, import, distribution and sale of medical devices require licenses or permissions, as the case may be.

Import, manufacture, sale and distribution of Medical devices are regulated under Drugs and Cosmetics Act, 1940; and Rules, 1945. At present following notified Medical Devices are regulated under the Act.

Further the following products are regulated as "Drugs" under Drugs and Cosmetics Act and Rules there under which are considered 'Medical Device' in the Country of Origin. This provision is ambiguous and inconsistent with Harmonized Standards of Medical Devices. Manufacture for

sale of these products is regulated by the concerned State Drug Licensing Authority only ²⁴.

AIM AND OBJECTIVE:

Aim:

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.

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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REFERENCES:

1. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 201
2. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 202
3. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p. 45
4. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 203-4
5. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 205-7
6. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 208-10
7. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p. 46

8. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p. 48
9. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 212-14
10. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 215-17
11. Rick NG. Drugs from discovery to approval. 2nd ed. John Wiley & Sons, Inc., (Hoboken, New Jersey). p. 218-20
12. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare. p. 49