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# Regulatory Requirements for the Drug Approval Process in US, Europe and India

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**Abstract:**

In the Current scenario, different countries have to follow different regulatory requirements for marketing authorization application (MAA) approval of new drug. In this present work, we studied the drug approval process and regulatory requirements according to US Food and Drug Administration (UDFDA), European Medical Agency (EMA) and Central Drug Standard Control Organisation (CDSCO).

**Key Words:** Drug Approval, Regulatory Requirements, USFDA, EMA, INDIA

## INTRODUCTION:

Currently different countries have to follow different regulatory requirements for approval of new drug. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. Therefore it is necessary to have knowledge about regulatory requirement for MAA of each country [1]. The basic regulation can be understood from **FIGURE 1.**

New drug application (NDA) is an application submitted to the respective regulatory authority for permission to market a new drug. To obtain this permission a sponsor submits preclinical and clinical test data for analyzing the drug information, description of manufacturing procedures.

Different Phases of clinical trials:

- Pre clinical study - Mice, Rat, Rabbit, Monkeys
- Phase I - Human pharmacology trial - estimation of safety and tolerability
- Phase II - Exploratory trial - estimation of effectiveness and short term side effects
- Phase III - Confirmatory trial - Confirmation of therapeutic benefits
- Phase IV - Post marketing trial - Studies done after drug approval[2,3,4].

After NDA received by the agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application.

At the conclusion of the review of an NDA, there are 3 possible actions that can send to sponsor:

- Not approvable- in this letter list of deficiencies and explain the reason.
- Approvable - it means that the drug can be approved but minor deficiencies that can be corrected like-labeling changes and possible request commitment to do post-approval studies.
- Approval- it state that the drug is approved.

If the action taken is either an approvable or a not approvable, then the regulatory body provides applicant with an opportunity to meet with agency and discuss the deficiencies[5,6].

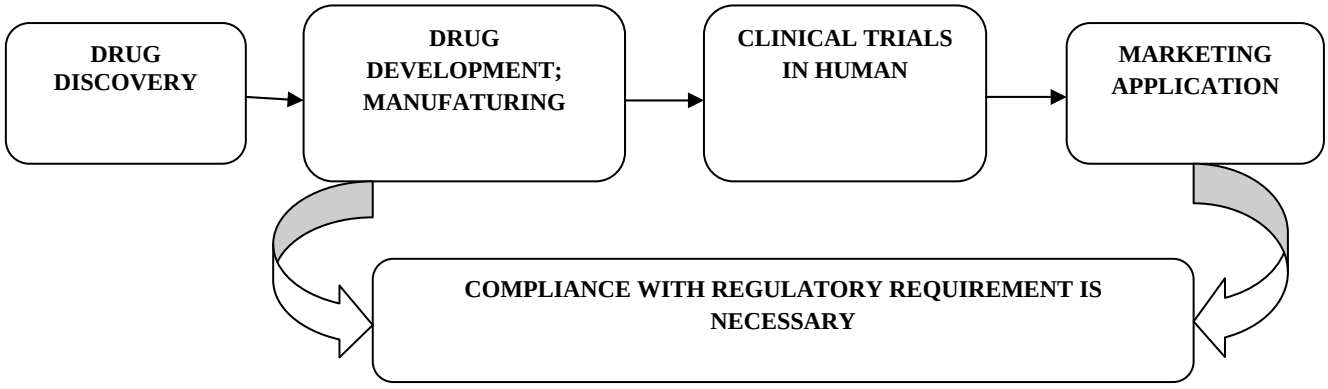


**FIGURE 1: Regulation of drug approval process**

## DRUG APPROVAL PROCESS IN UNITED STATES

In 1820, the new era of USA drug regulation was started with the establishment of U.S. Pharmacopoeia. In 1906, Congress passed the original Food and Drugs Act, which require that drugs must meet official standards of strength and purity [7]. However, in 1937, due to sulphanilamide tragedy, the Federal Food, Drug and Cosmetic Act (of 1938) was enacted and added new provisions that new drugs must be shown safe before marketing. Further, in 1962, the Kefauver-Harris Amendment Act was passed which require that manufacturers must prove that drug is safe and effective (for the claims made in labelling) [8,9].

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.

The Food and Drug Administration (FDA) is responsible for protecting and promoting public health. Like general drug approval process, FDA's new drug approval process is also accomplished in two phases: clinical trials (CT) and new drug application (NDA) approval. FDA approval process begins only after submission of investigational new drug (IND) application.

### 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. The IND application should provide high quality preclinical data to justify the testing of the drug in humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed. A firm or institution, called a Sponsor, is responsible for submitting the IND application.

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.

The next step is phase I clinical trials (1-3 years) on human subjects (~100). The drug's safety profile and pharmacokinetics of drug are focused in this phase. Phase II trials (2 years) are performed if the drug successfully passes phase I. To evaluate dosage, broad efficacy and additional safety in people (~300) are the main objective of the phase II. If evidence of effectiveness is shown in phase II, phase III studies (3-4 years) begins. These phase III concerns more about safety and effectiveness of drug from data of different populations, dosages and its combination with other drugs in several hundred to about 3,000 peoples [8].

### New drug application (NDA)

A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labelling. The preclinical, clinical reports and risk-benefit analysis (product's beneficial effects outweigh its possible harmful effects) are reviewed at the Centre for Drug Evaluation and Research by a team of scientists. 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 [9,10].

Generally approval of an NDA is granted within two years (on an average), however, this process can be completed from two months to several years. The innovating company is allowed to market the drug after the approval of an NDA and is considered to be in Phase IV trials. In this phase, new areas, uses or new populations, long-term effects, and how participants respond to different dosages are explored. **FIGURE 2** describes the drug approval process in USA

## DRUG APPROVAL PROCESS IN EUROPE

In European union (EU), the medical products were approved for marketing at the National level initially. The mutual recognization procedure was introduced in 1938 and a single national review in case of pharmaceutical/medicinal product for marketing authorization in EU's countries was made feasible. The primary aim of this procedure was to create a united standard for product review among national regulatory authorities. In 1987, for high-technology or biologically derived products, the concentration procedure was established by directive 87/22, in which product assessment should be completed by Committee for Proprietary Medicinal Products (CPMP) besides the normal national regulatory review. Further, in 1993, by council regulation (EEC) 2309/93, the concertration procedure was replaced with centralised procedure, by which all the high-tech and biologically derived product was reviewed and granted EU's wide marketing authorization by the EU's CPMP.

Similarly, the drug approval process in European countries is also accomplished in two phases: clinical trial and marketing authorization. A clinical trial application (CTA) is filed to the competent authority of the state to conduct the clinical trial within EU. The competent authority of that member state evaluates the application. The clinical trials are conducted only after the approval. The purpose and phases of clinical trials are similar as specified in FDA drug approval process. Figure 2 represent the clinical trial authorization process in EU.

After completing of all three phases of clinical trial, marketing authorization application (MAA) is filed including all animal and human data, its analyses, as well as pharmacokinetics, manufacturing and proposed

labelling. In the EU's countries, the company have a choice of following regulatory procedures:

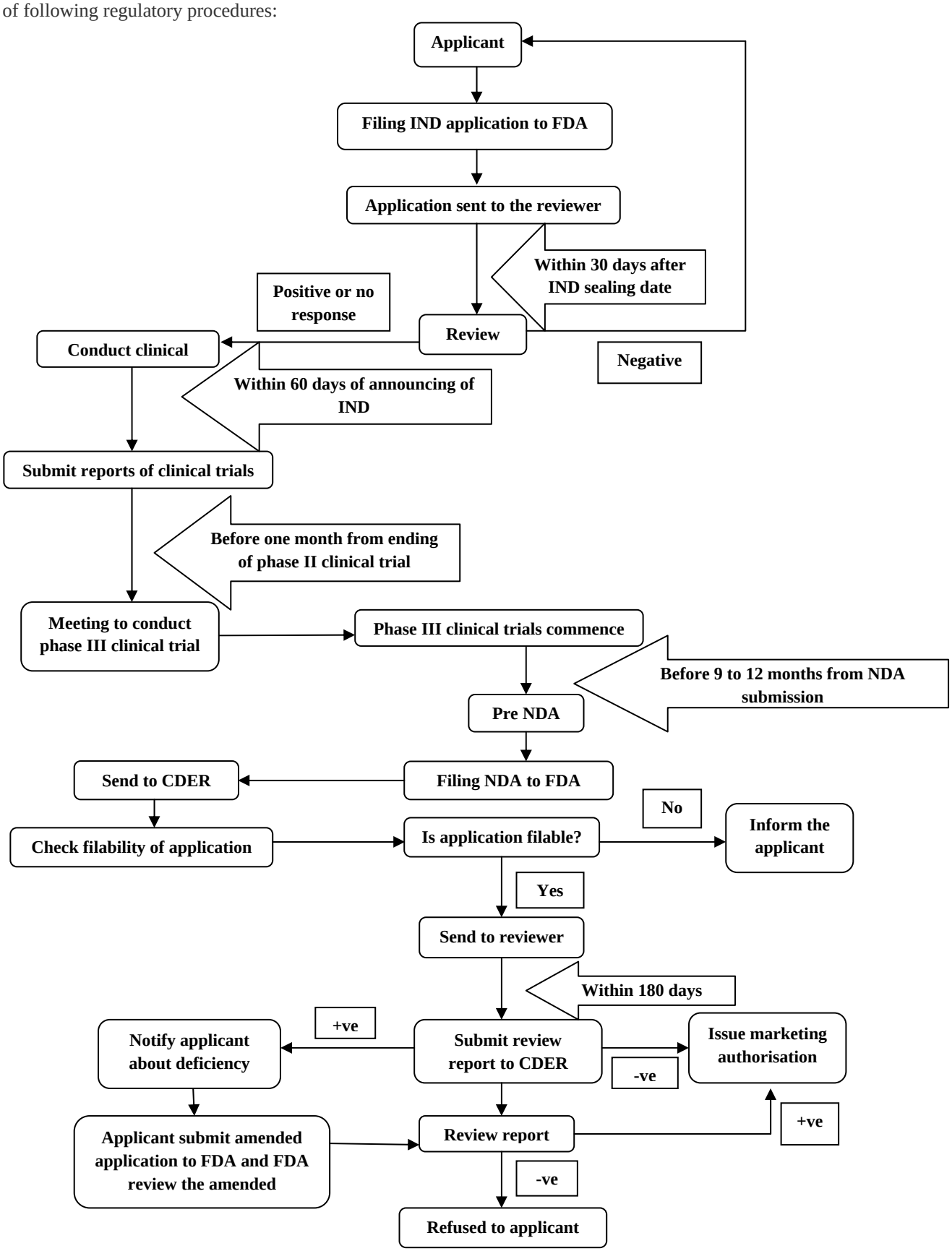


**FIGURE 2: Drug approval process in USA**

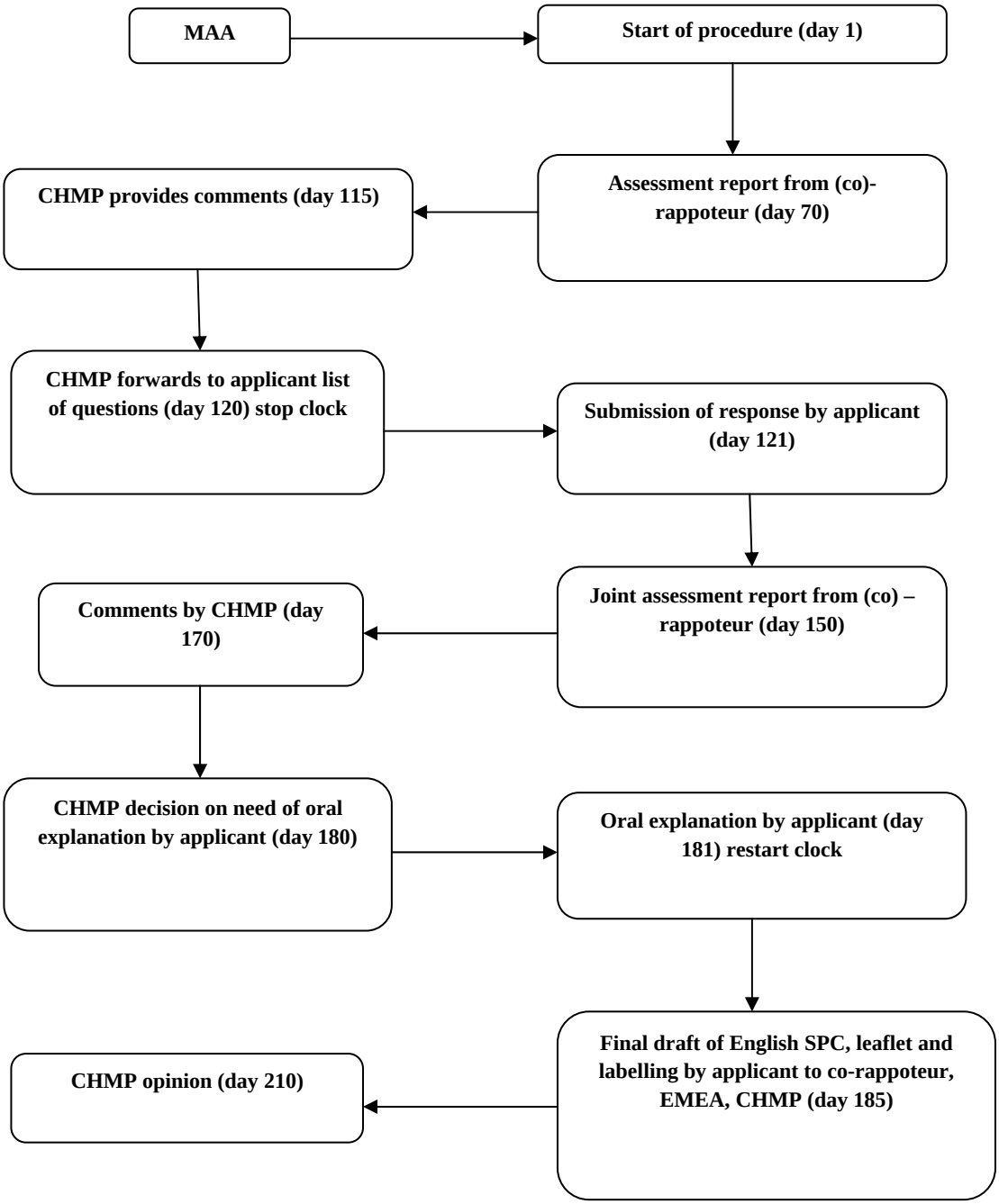


**FIGURE 3: Centralised procedure for marketing authorization in EU**

**Centralized Procedure**

The Committee for Human Medicinal Products (CHMP) evaluate the applications received by the EMEA. In view of the applicant's preference, CHMP contracts out assessment work in one of the member states (the "rapporteur"). After the complete assessment, the CHMP deliver opinion to EU Commission within 210 days [11]. The EU Commission requests comments from other member states, if a positive opinion from CHMP is received. The other member states can respond in about 28 days. When a licence is recommended, a European Public Assessment Report (EPAR) is produced and marketing authorisation is issued. This authorisation is valid throughout the European Union and is for five years, however, the extension can be applied to the EMEA three months before the expiration of this period. **FIGURE 3** represent the centralized procedure for marketing authorization.

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 [12].

- Medicines officially designated 'Orphan medicines' (medicines used for rare diseases).

**Decentralized Procedure**

In order to obtain marketing authorizations in several member states, the centralised procedure is not mandatory; in such case the decentralized procedure is to be used. An application is submitted to competent authorities of each of the member states, where a marketing authorization is to be sought. The information like quality, efficacy, safety, administrative information shall be submitted and a list of all Concerned Member States (CMSs) and one member state to act as Reference Member State (RMS). A draft assessment report on the medicinal product is prepared and the CMSs and the RMS validate the application within a time frame of 14 days. The RMS prepare draft summary of product characteristics, labelling and package leaflet within 120 days. This report can be approved within 90 days. However, if a medicinal product is supposed to cause potential serious risk to public health, CMS(s) will inform to other CMS, RMS and applicant and further decision in this regard is taken within 30 days. Within 60 days of the communication of the points of disagreement, all member states reach to an agreement on the action to be taken [13,14]. After reaching to an agreement of the member states, the RMS records the agreement and informs to the applicant. However, if the member states could not reach an agreement, then CHMP intervenes and take a final decision keeping in view of the written or oral explanations of the applicant. **FIGURE 4** represent the decentralized procedure for marketing authorization in EU.

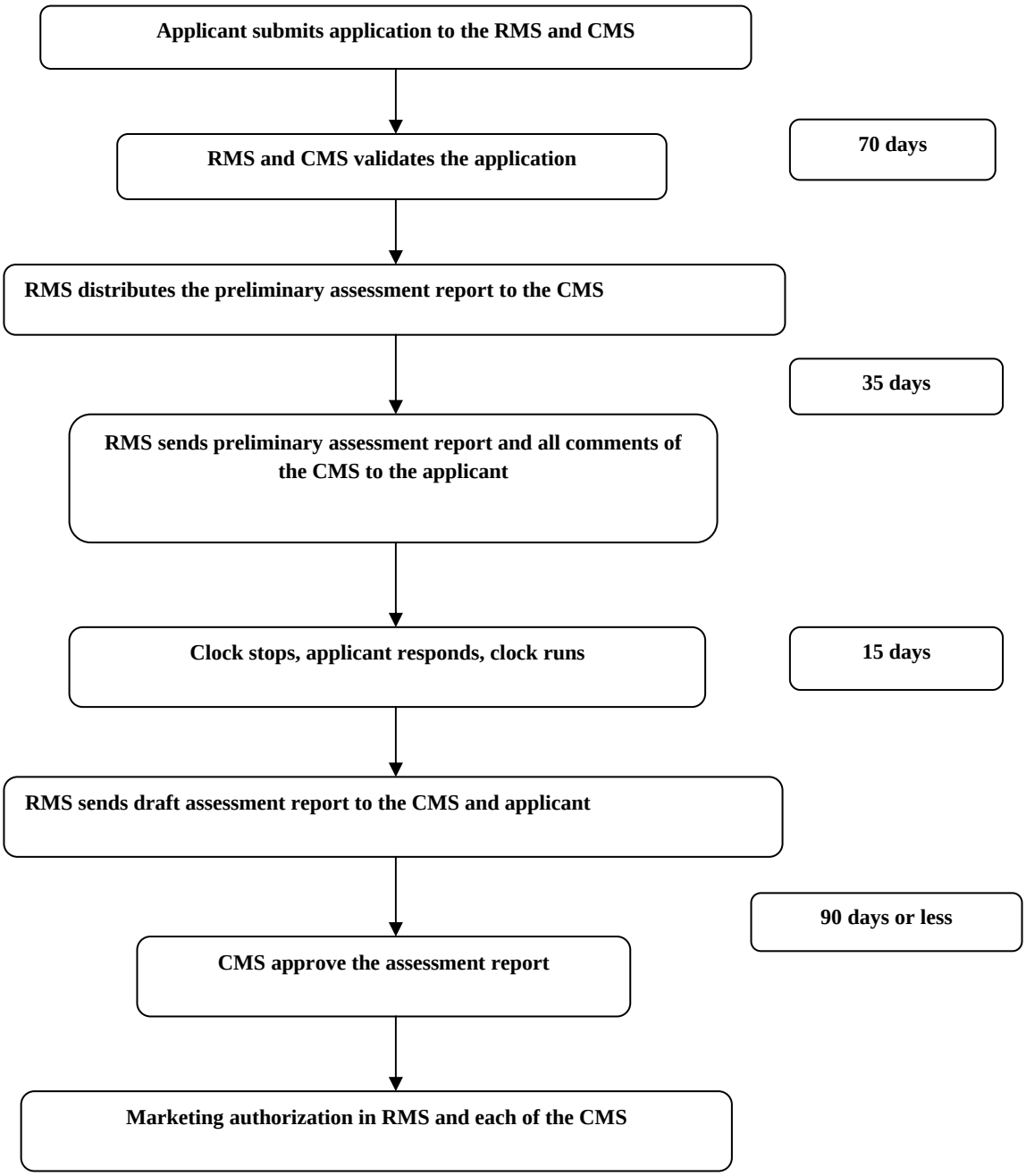


**FIGURE 4: Decentralised procedure for marketing authorization in EU**

**Nationalized Procedure**

The Nationalized procedure is one which allows applicants to obtain a marketing authorization in one member state only.

- 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

**Mutual Recognition Procedure**

The Mutual Recognition procedure allows applicants to obtain a marketing authorization in the concerned member states (CMS) other than the Reference member state (RMS), where the drug is previously approved [15].

- Applicant submits identical dossier to all EU member states in which they want marketing 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.

**FIGURE 5** represents the mutual recognition procedure for drug approval process in EU

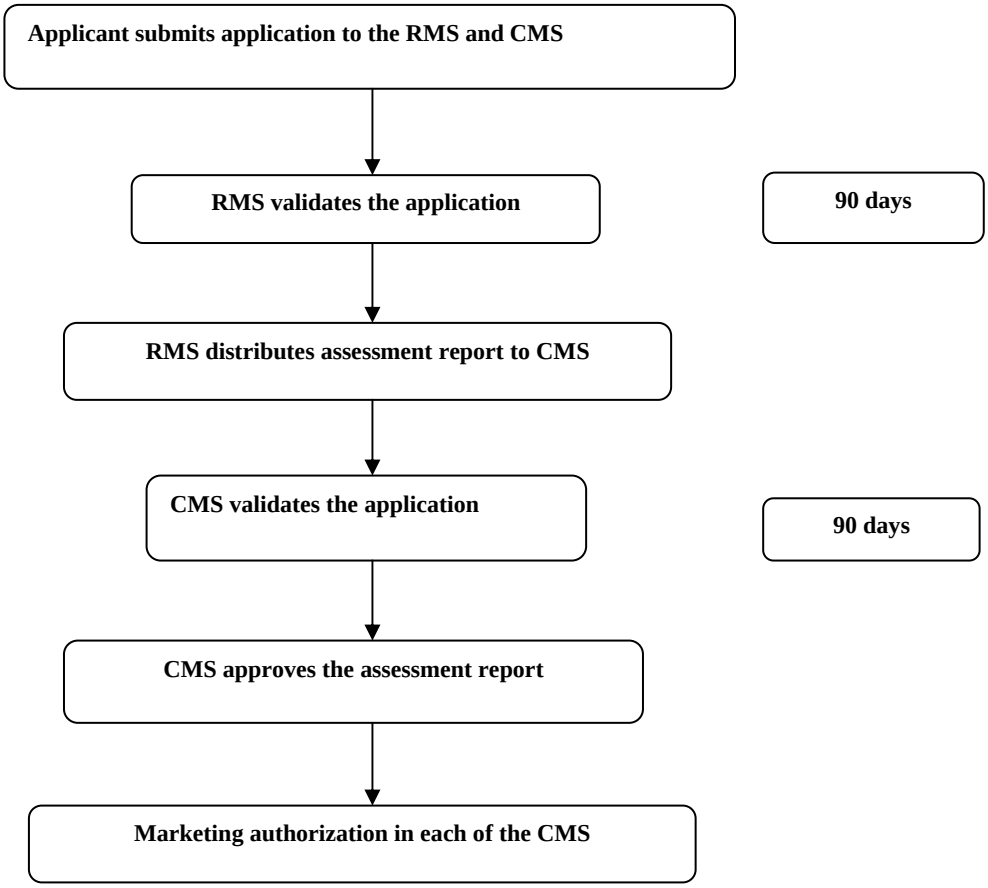


**FIGURE 5: Mutual recognition procedure for drug approval process in EU**

**DRUG APPROVAL PROCESS INDIA**

The Drug and Cosmetic Act 1940 and Rules 1945 were passed by the India's parliament to regulate the import, manufacture, distribution and sale of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO), and the office of its leader, the Drugs Controller General (India) [DCGI] was established. In 1988, the Indian government added Schedule Y to the Drug and Cosmetics Rules 1945. Schedule Y provides the guidelines and requirements for clinical trials, which was further revised in 2005 to bring it at par with internationally accepted procedure [16].

When a company in India wants to manufacture/ import a new drug it has to apply to seek permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its efficacy and safety in Indian population it has to conduct

clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format.
Rule- 122A of the Drug and Cosmetics Act says that the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries.

Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required.

Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials [17].

Demonstration of safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by Central Drugs Standard Control Organization (CDSCO). The regulations under Drugs and Cosmetics Act 1940 and its rules 1945, 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing [18].

The changes in the Drugs And Cosmetics Act includes, establishing definitions for Phase I-IV trials and clear responsibilities for investigators and sponsors. The clinical trials were further divided into two categories in 2006. In one category (category A) clinical trials can be conducted in other markets with competent and mature regulatory systems whereas the remaining ones fall in to another category (category B) Other than A. Clinical trials of category A (approved in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and European Union) are eligible for fast tracking in India, and are likely to be approved within eight weeks. The clinical trials of category B are under more scrutiny, and approve within 16 to 18 weeks [19].

An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI. The date regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached. A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee.

To determine the maximum tolerated dose in humans, adverse reactions, etc. on healthy human volunteers, Phase I clinical trials are conducted. The therapeutic uses and effective dose ranges are determined in Phase II trials in 10-12 patients at each dose level. The confirmatory trials (Phase III) are conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3-4 centers) to confirm efficacy and safety claims. Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centres, If the new drug substance is not marketed in any other country.

The new drug registration (using form # 44 along with full pre-clinical and clinical testing information) is applied after the completion of clinical trials. The comprehensive information on the marketing status of the drug in other countries is also required other than the information on safety and efficacy. The information regarding the prescription, samples and testing protocols, product monograph, labels, and cartons must also be submitted.

The application can be reviewed in a range of about 12-18 months. Figure 5 represents the new drug approval process of India. After the NDA approval, when a company is allowed to distribute and market the product, it is considered to be in Phase IV trials, in which new uses or new populations, long-term effects, etc. are explored. **FIGURE 6** describes the drug approval process in INDIA.

Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance has been developed for Japan, European Union, and United States.

Most countries have adopted the CTD format. Hence, CDSCO has also decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use.

Stages of approval [20,21,22]:
1. Submission of Clinical Trial application for evaluating safety and efficacy.
2. Requirements for permission of new drugs approval.
3. Post approval changes in biological products: quality, safety and efficacy documents.
4. Preparation of the quality information for drug submission for new drug approval.

The drug approval process varies from one country to another. In some countries, only a single body regulates the drugs and responsible for all regulatory task such as approval of new drugs, providing license for manufacturing and inspection of manufacturing plants e.g. in USA, FDA performs all the functions. However in some counties all tasks are not performed by a single regulatory authority, such as in India, this responsibility is divided on Centralised and State authorities. Some counties have two review processes as normal review process and accelerated review process as in USA, China etc. and some countries have only a single review process as in India. Similarly, the format used for the presentation of dossier submitted for approval of drug is also different. In some countries like as in USA, EU, and Japan , it is mandatory that the dossier

prepared in CTD format, however, in some countries it is optional such as in India.

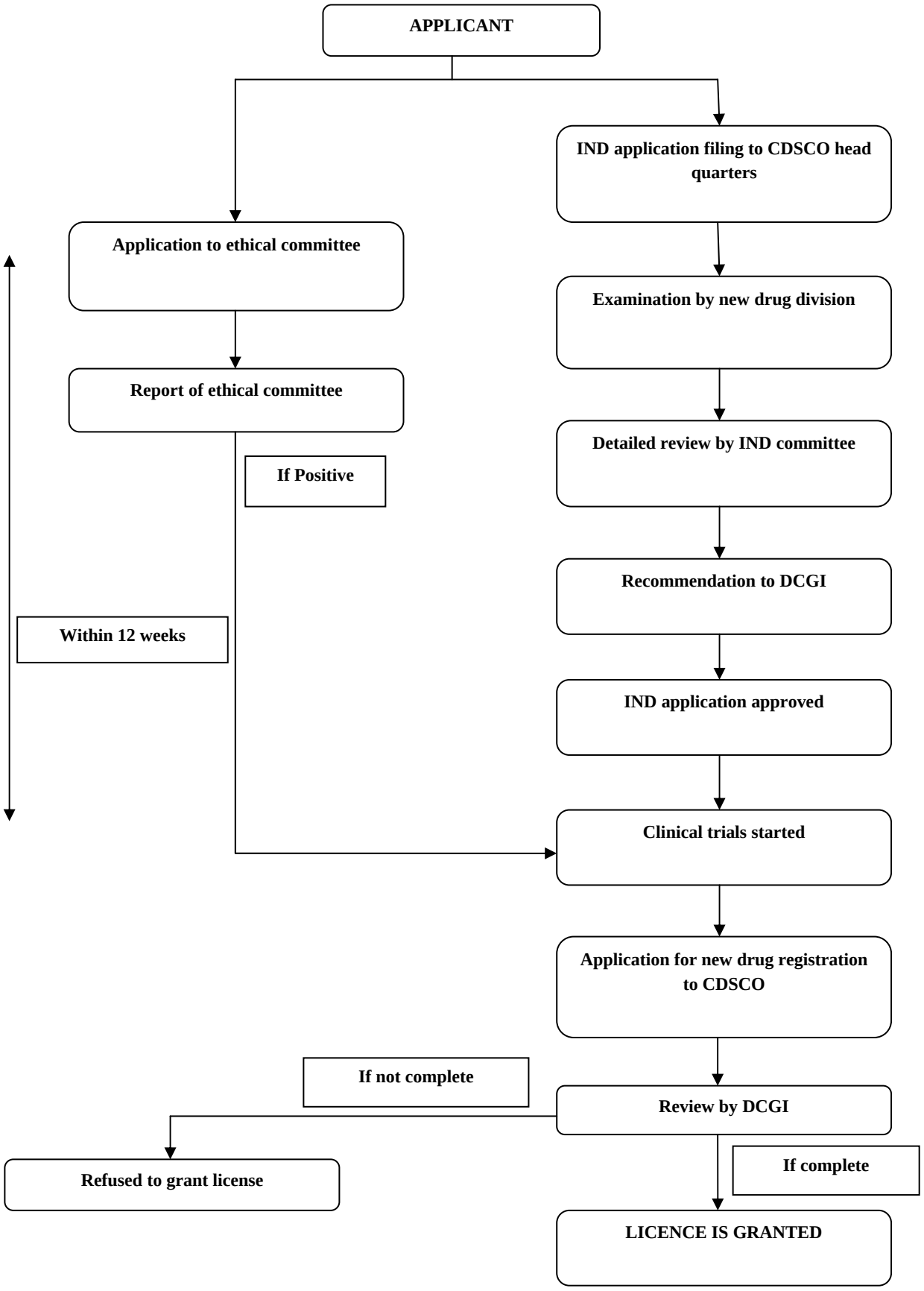


**FIGURE 6: D rug approval process in INDIA**

**TABLE 1: Principe difference between US, EU and INDIA**

| REQUIREMENTS | US | EU | INDIA |
|---|---|---|---|
| Agency | One agency USFDA | Multiple agencies<br>• EMEA<br>• CHMP<br>• National health agencies | One agency DCGI |
| Registration process | One registration process | Multiple registration process<br>• Centralised (European community)<br>• Decentralised (at least 2 member states)<br>• Mutual recognition (at least 2 member states)<br>• National (1 member state) | One registration process |
| TSE/BSE study data | Not required | Required | 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:<br>• Minor<br>• Moderate<br>• major | Post variation in the approved drug:<br>• Type IA<br>• Type IB<br>• Type II | Post approval changes:<br>• Major<br>• Moderate |

| REQUIREMENTS | US | EUROPE | 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 | 2 - 18 months |
| Fees | Under $2 million – NDA application<br>$1,520 – ANDA application | National fee (including hybrid applications): £103,059<br>Decentralised procedure where UK is CMS:£99,507 | 50,000 INR |
| Presentation | eCTD and paper | eCTD | Paper |

**TABLE 2: Administrative requirements**

**TABLE 3: Manufacturing and control requirements**

| REQUIREMENTS | US | EUROPE | INDIA |
|---|---|---|---|
| Number of batches | 1 | 3 | 1 |
| Packaging | A minimum of 1,00,0000 | 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 |

## DISCUSSION

Generally, the drug approval process comprised mainly the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug. The new drug approval process of various countries is similar in some of the aspects whereas it differs in some aspects. In most of the counties, sponsor firstly files an application to conduct clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is similar; however, the time,

fee and review process of clinical trials and marketing authorization application differs. For the purpose of harmonisation, the International Conference on Harmonisation (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements. Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance has been developed for Japan, European Union, and United States. Hence, India also follows the same.

This step will ultimately reduce the need to duplicate work carried out during the research and development of new drugs. Therefore, harmonization of drug approval processes either by ICH or WHO may be initiated at global level.

The regulatory agency for US and INDIA is a single agency i.e. USFDA and CDSCO respectively, whereas in EUROPE, there are three regulatory agencies, they are EMEA, CHMP and NATIONAL HEALTH AGENCY. Europe also has multiple regulatory procedures when compared to US and INDIA. The approval time in all the countries is almost the same i.e., 12 to 18 months. The fee for the new drug approval in US is very high when compared to EUROPE and INDIA.

## CONCLUSION

The Drug approvals in the US, Europe & India are the most demanding in the world. The primary purpose of the rules governing medicinal products in US, Europe & India 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, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

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