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Review Article

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Drug approval process in US, Europe and India and its regulatory requirements: A Review

Krishnasis Chakraborty*, Kavita Yadav

Department of Quality Assurance, Al-Ameen College of Pharmacy, Lalbagh road, Bangalore, India.

ABSTRACT

Current constrain of Regulatory Affairs reveals diverse countries need to follow different regulatory requirements for marketing authorization Application (MAA) approval of new drugs. In this present exertion, study expresses the drug approval process and regulatory requirements according to US Food and Drug Administration (UDFDA), European Medical Agency (EMA) and Central Drug Standard Control Organization (CDSCO) (1).

Keywords: Drug Approval, Regulatory Requirements, USFDA, EMA, CDSCO, DCGI.

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Corresponding author Tel.: +91-9632703191;

E-mail address: krishnasis07p@gmail.com (Krishnasis Chakraborty).

1. Introduction

Presently different countries must follow different regulatory requirements for sanction of new drug. Marketing Authorization Application (MAA) a single regulatory approach is valid to various countries is almost a difficult task. Therefore, it is essential to have knowledge about regulatory requirement for MAA of each country.

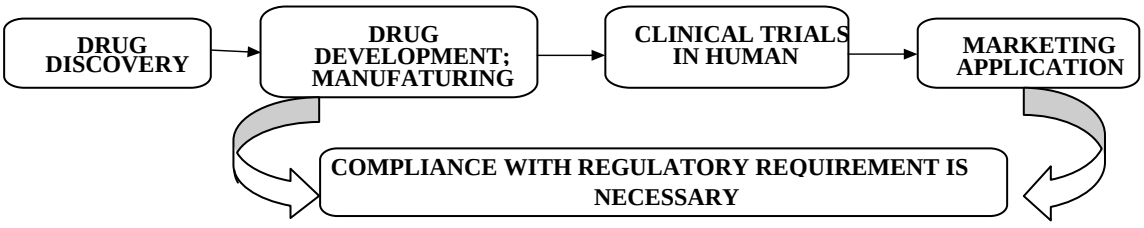

Figure 1. Regulation of Drug Approval Process (1-6)

New drug application (NDA) is an application submitted to the individual regulatory authority for authorization to market a new drug i.e. innovative product. To gain this permission a sponsor submits preclinical and clinical test data for analyzing the drug information, description of manufacturing trials (2-4).

Different Phases of clinical trials

- ❖ Pre-clinical study
- ❖ Phase I - Clinical trial
- ❖ Phase II - Exploratory trial
- ❖ Phase III - Confirmatory trial
- ❖ Phase IV - Post marketing trial

After NDA received by the agency, it endures a technical transmission. This assessment confirms that adequate data and information have been submitted in each area to justify "filing" the application.

After review of an NDA, there are 3 conceivable actions that can send to applicants:

- ❖ Not approvable- Regulatory deficiencies and clarify the reason.

- Approvable - Drug can be approved but minor deficiencies that can be amended like-labeling changes and commitment or to do post-approval studies.
- Approval- Drug is approved.

If the action taken is either an approvable or a not approvable, then the regulatory body offers applicant with an opportunity to meet with agency and discuss the deficiencies (5-7).

2. Drug Approval Process in United States

In 1820, USA drug regulation was started with the establishment of U.S. Pharmacopoeia.

In 1937, due to Sulphanilamide tragedy, the Federal Food, Drug and Cosmetic Act (of 1938) was enacted and supplementary new provisions that new drugs must be shown harmless before marketing.

Additional, in 1962, the Kefauver-Harris Amendment Act was passed which require that manufacturers must demonstrate that drug is safe and effective (for the claims made in labelling) (8).

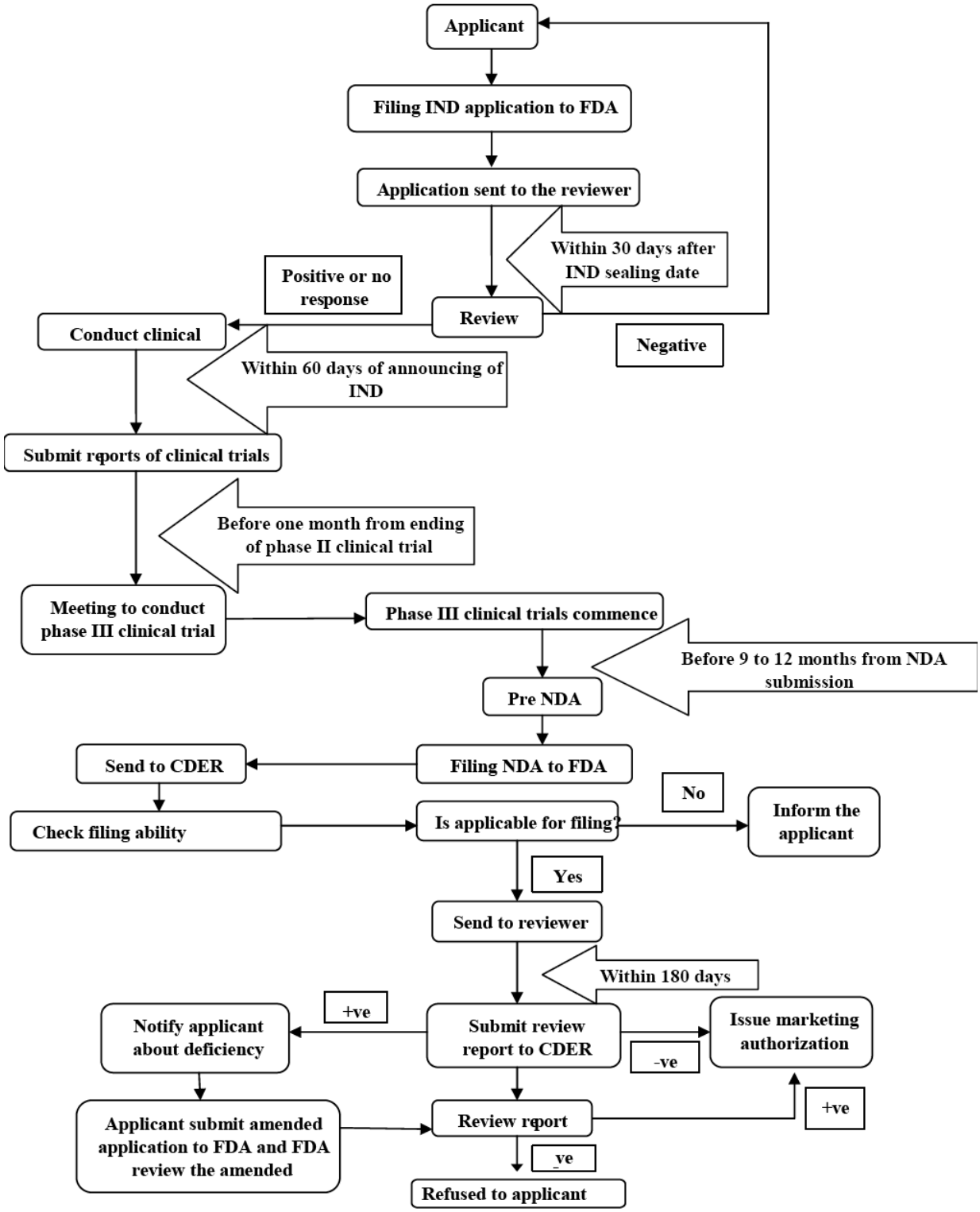

Figure 2. Drug Approval Process in United State (9-11)

The United States has believably 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 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 excellence 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. An institution, called a Sponsor, is responsible for submitting the IND application (9,10).

A Pre - IND assessment can be organized with the FDA to deliberate multiple 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.

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 comprises all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and anticipated labelling. The preclinical, clinical reports and risk-benefit analysis are studied at the Centre for Drug Evaluation.

If clinical studies confirm that a new drug is comparatively safe and effective, and will not pose irrational risks to patients, the manufacturer files a New Drug Application (NDA), the actual request to manufacture and can market the drug in the United States.

Generally, approval of an NDA is granted within two years, however, this process can be finalized from two months to several years. The innovating company is permitted 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 (11).

3. Drug Approval Process in Europe

In European Union (EU), the medical products were approved for marketing at the National level initially. The mutual recognition process was introduced in 1938 and a single national review in case of pharmaceutical/ medicinal products for marketing authorization in EU countries.

The prime purpose of this procedure was to create a united standard for product review among national regulatory authorities. In 1987, for high-technology or biologically derivative products, the concentration procedure was established by directive 87/22, in which product valuation should be finalized by Committee for Proprietary Medicinal Products (CPMP) as well the normal national regulatory evaluation. Further, in 1993, by council regulation (EEC) 2309/93, the awareness procedure was replaced with centralized 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. Correspondingly, 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 countries. The competent authority of that member state reviews the application. The clinical trials are conducted only after the approval. The purpose and phases of clinical trials are analogous as specified in FDA drug approval process.

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

Centralized Procedure

The Committee for Human Medicinal Products (CHMP) evaluates the applications received by the EMEA. In view of the applicant's preference, CHMP agreements out assessment work in one of the member states ("Rapporteur"). After the complete assessment, the CHMP deliver opinion to EU Commission within 210 days. The EU Commission appeals remarks from other member states, if a positive opinion from CHMP is acknowledged. The other member states can respond in about 28 days. When a license is recommended, a European Public Assessment Report (EPAR) is produced and marketing authorization is issued. This authorization is indorsed 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 (12,13).

Centralized process is compulsory for:

- Biotechnology processed medicines, such as genetic engineering.
- Medicines for treatment of Cancer, HIV/AIDS, diabetes, neurodegenerative disorders and other immune dysfunctions.
- Medicines officially nominated 'Orphan medicines'.

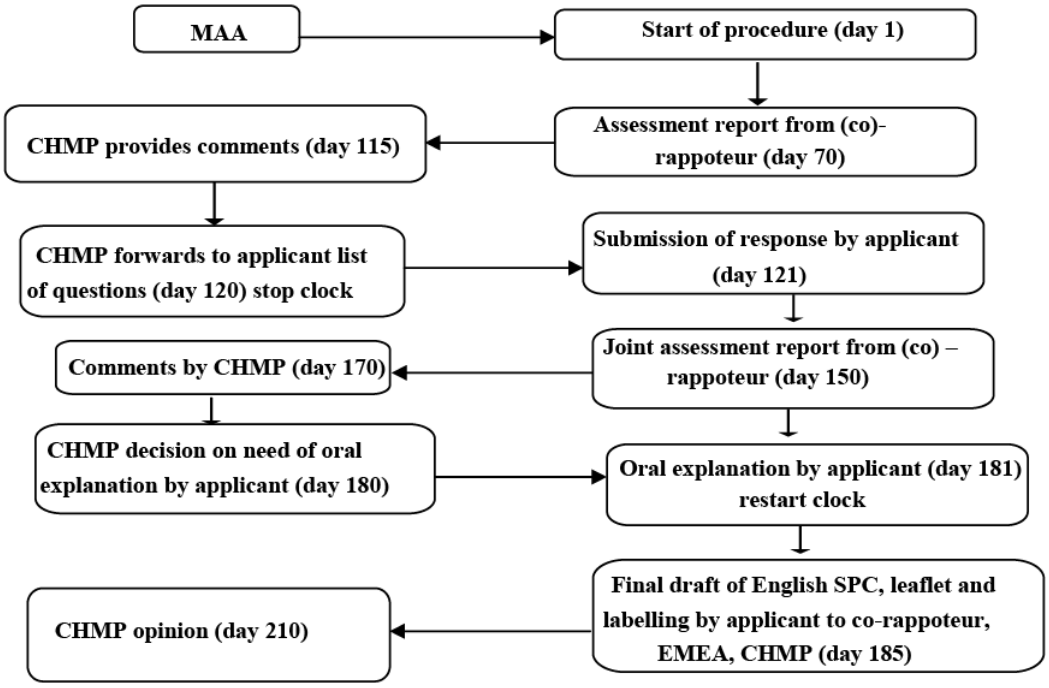

Figure 3. Centralized Procedure for Marketing Authorization in EU (12)

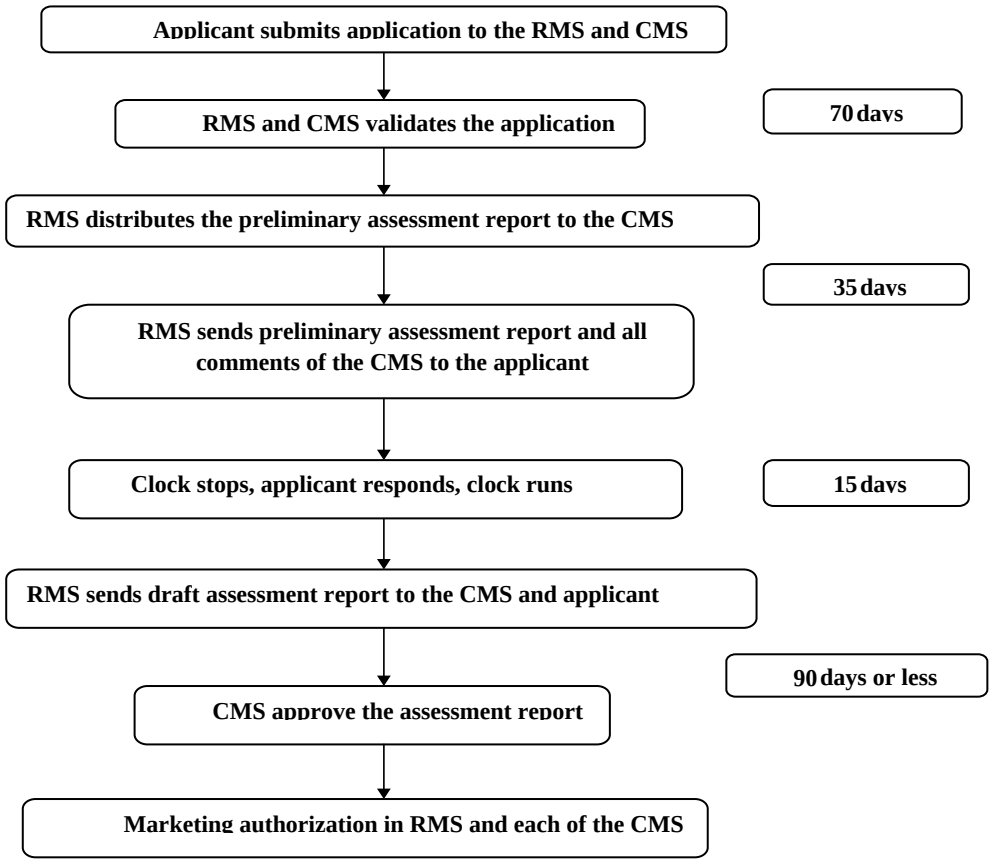

Figure 4. Decentralized Procedure for Marketing Authorization in EU (12,13)

Decentralized Procedure

To receive marketing authorizations in numerous member states, the centralized 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 required. 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 CMS and the RMS confirm 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 will inform to other CMS, RMS and applicant and further conclusion in this regard is taken within 30 days. Within 60 days of the announcement of the points of disagreement, all member states reach to an agreement on the action to be taken.

After a conclusion 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.

Nationalized Procedure

The Nationalized procedure is one which permits applicants to receive a marketing authorization in one-member state only.

- 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 entire process 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 (14-16).

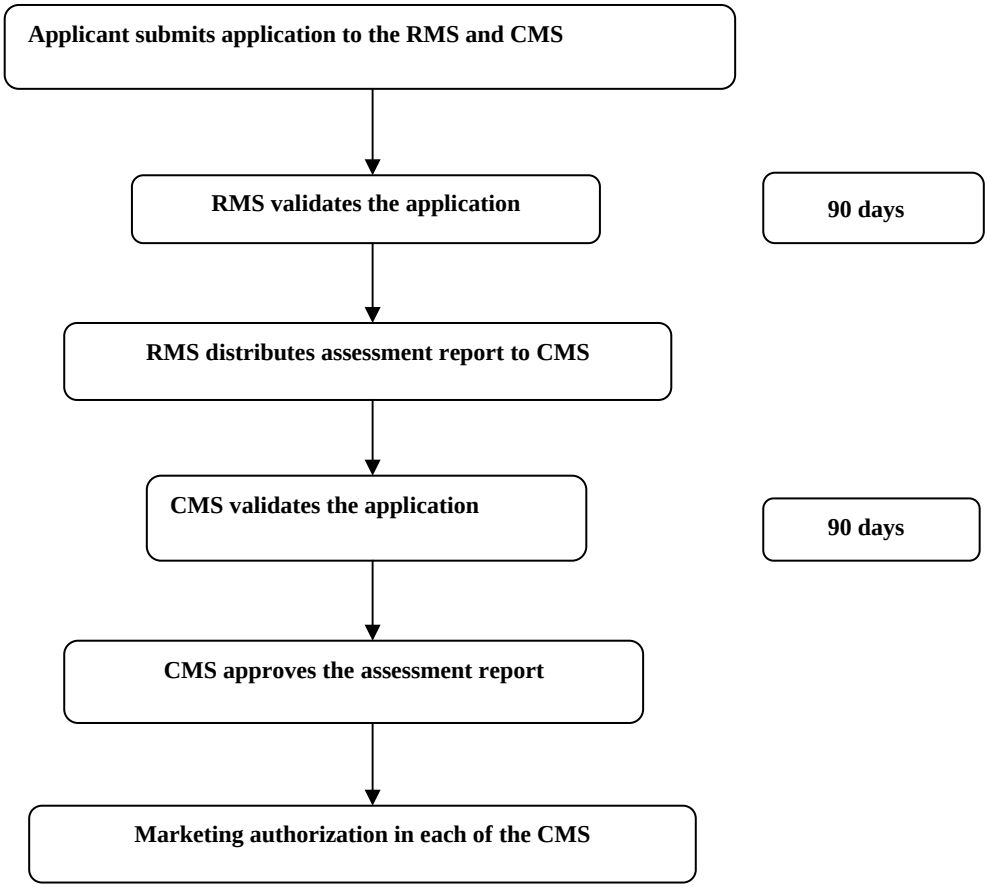

Figure 5. Mutual Recognition Procedure for Drug Approval Process in EU (12-16).

4. Drug Approval Process in India

The Drug and Cosmetic Act 1940 and Rules 1945 were proclaimed 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 (DCGI) was established (17).

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 reviewed in 2005 to bring it at par with worldwide recognized procedure.

When a company in India wants to manufacture/ import a new drug, must 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. To demonstrate its efficacy and safety in Indian population, must conduct clinical trials in accordance with the guidelines specified

in Schedule Y and submit the report of such clinical trials in specified format (18).

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 compulsory.

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 presented from other countries and the licensing authority may necessitate to replication all the studies or permit him to proceed from Phase III clinical trials.

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.

The changes in the Drugs and Cosmetics Act includes, launching 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 clinical trials can be conducted in other markets with competent and established regulatory systems whereas the remaining ones fall in to another category other first category.

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 regulate the maximum tolerated dose in humans, adverse reactions, 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 approximate 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 centers, If the new drug substance is not marketed in any other country (19,20).

After the NDA approval, when an Organization can 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.

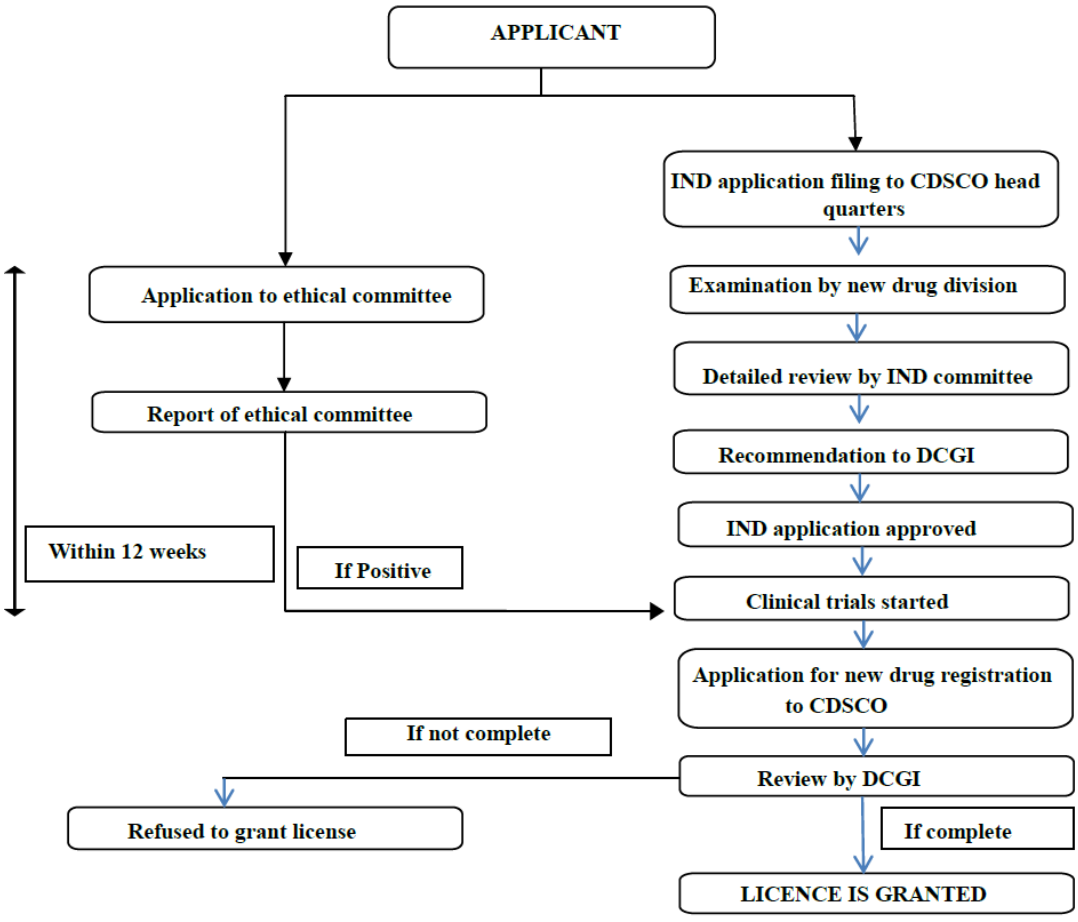

Figure 6. Drug Approval Process in India (19-23)

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

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

- ❖ Submission of Clinical Trial application for evaluating safety and efficacy.
- ❖ Requirements for authorization of new drugs approval.
- ❖ Post approval changes in biological products: quality, safety and efficacy documents.
- ❖ 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 Centralized and State authorities. Some counties have two review processes as normal review process and accelerated review process as in USA and some countries have only a single review process as in India. Similarly, the format used for the demonstration of dossier submitted for approval of drug is also dissimilar. In some countries like as in USA, EU, Canada and Japan, it is mandatory that the dossier should be represented in eCTD format only (21-23).

5. Discussion

The drug approval process included 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 varies 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 applies 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. To harmonize, the International Conference on Harmonization (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 United States, European Union, Canada, Japan and other countries. Hence, India also tracks 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 USA 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.

Table 1 Principe transformation between US, EU and 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 • Centralised (European community) • Decentralised (at least 2 member states) • Mutual recognition (at least 2 member states) • 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: • Minor • Moderate • major	Post variation in the approved drug: • Type IA • Type IB • Type II	Post approval changes: • Major • Moderate
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	2 - 18 months
Presentation	eCTD and paper	eCTD	Paper

Table 2 Manufacturing and control requirements

Requirements	US	EU	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 scales plus 1 lab batch or minimum of 1 lakh units whichever is higher	Pilot scale batch

6. Conclusion

The Drug endorsements in the USA, Europe, Canada, Japan & India are the most challenging in the world. The primary purpose of the rules governing medicinal products in USA, Europe, Canada, Japan and India is to precaution 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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Conflict of interest

The authors declare that there are no conflicts of interest.

References

1. Rick NG. Drugs from discovery to approval. New Jersey: John Wiley & Sons; 2015.
2. IRA R Berry, Robert P Martin, editors. The Pharmaceutical Regulatory Process. 2nd ed. Informa healthcare: 45; 2002 Dec 02.
3. Kuhlmann J. Int. Journal of Clinical Pharmacology and Therapeutics. 1999; 37(12):575-83.
4. Bhatt A. Indian Journal of Pharmacology. 2004; 36(4):207-8.
5. CDER Guidance. A review for OCRA US RAC Study [Internet]. US FDA 2012 [cited 2018 May 25]. Available from: https://www.fda.gov/cder/regulatory/applications/
6. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Med. J. 2004; 181:293-4.
7. Ed Miseta. What You Need to Know About FDA's Clinical Outcome Assessment Compendium [Internet]. [cited 2018 Jan 06]. Available from: https://www.clinicalleader.com/doc/what-you-need-to-know-about-fda-s-clinical-outcome-assessment-compendium-
8. U.S. Food and Drug. Law History [Internet]. US FDA; 2005 [cited 2018 Mar 10]. Available from: https://www.fda.gov/AboutFDA/WhatWeDo/History/Milestones/ucm128305.html.
9. Lipsky MS and Sharp LK. J Am Board Fam Pract. 2001; 14:362-7.
10. Jawahar N, Prashob Nair A, Ramachandran. Pharma Times. 2015; 47(1):35-9.
11. Food and Drugs: Chapter I-Food and Drug, Title 21: PART 312- Investigational New Drug Application [Internet]. 2003 [cited 2018 May 11]. Available from: https://www.access.gpo.gov/nara/cfr/waisidx_03/21cfr312_03
12. Jawahar N, Shrivastava N, Ramachandran, Priyadharshini RB. J. Pharm. Sci. & Res. 2015; 7(4):219-25.
13. U. Nitin Kashyap, Vishal Gupta, H V Raghunandan. J. Pharm. Sci. & Res. 2013; 5(6):131-6.
14. European Commission: The Notice to Applicants; Volume 2A; Procedures for marketing authorization [Internet]. EMEA; 2004 [cited 2018 Mar 15]. Available from: http://ec.europa.eu/health/files/eudralex/vol-2/a/vol2a_chap1_2005- 11
15. EMA. Guideline on non-clinical local tolerance testing of medicinal products [Internet]. EMEA; 2015 [cited 2018 Jan 10]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/document/
16. Ghalamkarpour A. Marketing Authorization Procedures in the European Union - Making the Right Choice [Internet]. 2009 Dec [cited 2018 Jun 10]. Available from: https://www.sgsgroup.fr/~/media/Global/Documents/Technical%20Documents/SGS-Clinical-Marketing-Authorization-EN-09.pdf
17. Regulatory requirements. Timeline for approval [Internet]. 2005 [Cited 2018 Feb 02]. Available from: www.clinpage.com/article/indias_regulation_timeline/C9.
18. Technical Guidance on Development of In vitro Companion Diagnostics and Corresponding therapeutic Products [Internet]. PMDA; 2013 Dec 26 [Cited 2018 Jan 10]. Available from: https://www.pmda.go.jp/files/000153149.pdf
19. Vishal Gupta N, Mohan Reddy C, Pradeep Reddy K, R Ajay Kulkarni, Shivakumar HG. Process of Approval of New Drug in India with Emphasis on

Clinical Trials. International Journal of Pharmaceutical Sciences Review and Research. 2012; 13(2):17-23.

20. Honorio S. Phases of drug development; Good practices in clinical research [Internet]. [cited 2018 May 26]. Available from: http://www.hstelearning.mit.edu.
21. Ravinder RB, Suresh N. Regulatory stages for New Drug approvals [Internet]. [cited 2018 Jan 07]. Available from: https:// www.observerindia.com/cms/export/orfonline /modules/occasionalpaper/attachments/Drug_Discovery_ Book_1260179432814.pdf
22. Lachman L, Liberman HA, Kanig JL. The Theory and Practice of Industrial Pharmacy. Varghese Publishing House; 1987.
23. The drug development and approval process Overview of the process [Internet]. 2011 [cited 2018 Mar 03]. Available from: http://www.mhsource.com/resource/process.html.