Available online on 15 June, 2020 at https://ijdra.com/index.php/journal

International Journal of Drug Regulatory Affairs

Published by Diva Enterprises Pvt. Ltd., New Delhi
Associated with Delhi Pharmaceutical Sciences & Research University

Review Article

Overview of Drug Regulatory Affairs and Drug approval process in US, Europe, India and Canada: A Review

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Abstract

Pharmaceutical drug regulatory affairs issues administer enlistment parameters of pharmaceutical products. It has an expansive range covering all parts of documentation and marketing in legitimized structure. DRA is a dynamic, remunerating field that incorporates both logical and lawful parts of medication advancement. DRA experts are committed people who invest heavily in their commitment to improving the health and quality of life of peoples. RA as calling is more extensive than enlistment of product; they prompt organizations both deliberately and actually at the most significant level.

Today, the administrative necessities for approval of another medication in the different nations of the world are very extraordinary. To create one single administrative methodology for marketing authorization application (MAA) of another medication product for different nations is most extreme troublesome assignment particularly for organizations with worldwide exercises. In this manner, it is imperative to know in detail the administrative necessities in every nation where a MAA ought to be submitted to build up an appropriate administrative technique before the accommodation so as to stay away from any significant troubles. The new medication approval is of two stage process, clinical preliminaries stage and Marketing approval of medication. This review article depends on procedures for drug approval in different countries like India, USA, Europe and Canada.

Keywords: Drug regulatory affairs, MAA, USFDA, CDSCO, EMA, Notice of Compliance (NOC), Notice of Deficiency (NOD), RMS, CMS, ANDA

Article Info: Received 21 May. 2020; Review Completed 14 Jun. 2020; Accepted 15 Jun. 2020

Cite this article as:
Patil A and Thakre A. Overview of Drug Regulatory Affairs and Drug approval process in US, Europe, India and Canada: A Review. International Journal of Drug Regulatory Affairs [Internet]. 15 Jun 2020 [cited 15 Jun 2020]; 8(2):36-43. Available from:
http://ijdra.com/index.php/journal/article/view/401

DOI: 10.22270/ijdra.v8i2.401
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1. Introduction

A medication Regulatory undertaking is an extension between pharmaceutical industry and administrative body. Administrative Affairs is a calling which is started from governments to ensure general wellbeing, by controlling the security and viability of items in regions including medications, pharmaceuticals, clinical gadgets, pesticides, agrochemicals, beauty care products and integral prescriptions. The organization must guarantee that the item which is assembling and market is of acceptable quality for general wellbeing and welfare. (1) The present Pharmaceutical Industry is well precise, sorted out and consistent to worldwide administrative measures for assembling of Biological medications and compound for human and veterinary utilization just as clinical gadgets, beautifying agents and conventional home grown items. (2)

During 1950s, different disasters for example sulfanilamide solution, immunization disaster and thalidomide catastrophe have brought about considerable increment of enactments for medicate items quality, security and adequacy. This has additionally come about into stricter standards for Marketing Authorization (MA) and Good Manufacturing Practices (GMPs). (3) Stringent GMPs are being followed for blood and its subsidiary just as controlled assembling for Traditional Herbal Medicines, Food and Dietary items and Cosmetics which was in any case distinctively a century prior. Each administrative framework had confronted certain conditions which prompted current all-around characterized controlled administrative system. This has come about into methodical assembling and showcasing of protected, viable and subjective medications. (4) One of the imperative exercises of the administrative authority is to guarantee that the all the data with respect

to medications has been effectively settled to the patient covering naming too. Indeed, even a little misstep in any of the exercises identified with administrative can make the product to be reviewing notwithstanding loss of a few a great many the cash. (4)

Importance of regulatory affair

A decent Regulatory Affairs expert will have a significant impact in planning logical Endeavor with administrative requests for the duration of the life of the item, assisting with amplifying the savvy utilization of the organization's assets. (5)

In this Global competitive environment the time taken by the product to reach the market is critical parameter and hence the company's success relies on that. The proper control maintain of its Regulatory Affairs activities is therefore of considerable economic importance for the company. Regulation is a binding instruction issued by an agency that tells how to interpret and comply with a law. If any fails to follow the regulations may end up in the "issued warning letter" section of the FDA website, which is not a good for a Pharmaceutical company. In this way, Regulatory Affairs department is the first point of contact between the Ministry of Health /Government departments and the company. (1)

Objectives of regulatory affairs (2, 4)

1. Roles of Regulatory Affairs Professional in Health Authorities as well as Pharmaceutical Industry
2. Ensuring that their companies comply with all of the regulations and laws pertaining to their business
3. Working with federal, state and local regulatory agencies and personnel on specific issues affecting their business
4. Advising companies on the regulatory aspects and climate that would affect their proposed activities
5. Indian Pharmaceutical Industry & Drug Regulations development in different Era

Drug Approval procedure in different countries

For approval of new drug different countries have to follow different regulatory requirements. For marketing authorization application (MAA) a solitary administrative methodology is material to different nations is just about a troublesome assignment. Thusly it is important to know about administrative necessity for MAA of every nation. It is difficult to go for a single regulatory approach for approval of a new drug in different countries therefore each country has its own regulatory requirements which have to be satisfied to approve a new drug in that particular country. Hence there is a need for gaining awareness on regulatory issues of various countries. (6, 7) Firstly, when a lead molecule is identified for a target disease, it should be optimized. After the discovery of a drug, pre-clinical trials are conducted on animals to ensure safety and efficacy. An application should be submitted to competent authority of a concerned country to get permission for conducting clinical studies. Clinical trials are performed in four phases to assure safety, efficacy and then the drug dose is optimized in humans. A Marketing Authorization Application (MAA) is then submitted, which is approved by the competent authority, if the drug satisfies the requirements of safety and efficacy and proves that its benefits outweigh its risks. New Drug Application (NDA) is an application which is 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 analysing the drug information, description of manufacturing trials.

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

This assessment confirms that adequate data and information have been submitted in each area to justify "filing" the application.

Table 1. Regulatory bodies in different countries

Country	Regulatory body
India	Central Drug Standard Control Organization (CDSCO)
USA	Food and Drug Administration (FDA)
Europe	European Medicines Agency (EMEA)
Canada	Health Canada
Japan	Ministry of Health, Labour & Welfare(MHLW)

Investigational New Drug (IND) Application (8,9)

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

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

New Drug Application (NDA)

New drug application is application to the regulatory authority to manufacture and sell the drug in the respected area. NDA filed when clinical studies confirm that a new drug is relatively safe and effective, non-toxic and will not pose unreasonable risks to patients.

Contents and Format of NDA Two copies of the application are: (a) Archival copy and (b) Review copy.

a) Archival Copy: It serves as a reference source for FDA reviewers to locate information not contained in the

review copy; and it contains copies of tabulations and clinical study case report forms. It contains the following elements:

1. Application form FDA 356
2. Index
3. Summary
4. Technical sections: further typed to
5. Chemistry, manufacturing and controls section
6. Non-clinical pharmacology and toxicology section
7. Human pharmacokinetics and bioavailability section
8. Microbiology section
9. Clinical data section
10. Statistical section
11. Pediatric use section
12. Samples and Labeling
13. Case report forms

b) Review Copy: Each technical section is separately bound in each folder. Each technical sect ion should contain:

1. Index
2. Copy of FDA Form 356 h
3. Copy of cover letter
4. Letters of authorization
5. Copy of application summary 9 (10)

Abbreviated New Drug Application (ANDA)

For approval of generic drug this application was required. The support isn't required to reproduce the clinical examinations that were accomplished for the first, brand name item. Rather, nonexclusive medication makers must exhibit that their item is equivalent to, and bioequivalent to, a formerly approved brand name item.

2. Drug Approval Process in India (10)

The Drug and Cosmetic Act 1940 and Rules 1945 were announced by the India's parliament to direct the import, production, circulation and offer of medications and cosmetics. The Central Drugs Standard Control Organization (CDSCO) and the office of its leader, the Drugs Controller General (DCGI) was established.

The clinical trials can be registered in the Clinical Trials Registry of India (CTRI) giving details of the clinical trials and the subjects involved in the trials. The rules to be followed under The Drugs and Cosmetics Rules 1945 are:

1. Rule 122 - A: Application for permission to import new drug
2. Rule 122- B: application for approval to manufacture new drug other than the drugs specified under Schedule C and C.
3. Rule 122 - D: Permission to import or manufacture fixed dose combination.
4. Rule 122 - DA: Application for permission to conduct clinical trials for New Drug/Investigational New Drug.
5. Rule 122 - DAB: Compensation in the case of injury or death during the clinical trials.

The applicant submits the application to the ethical .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 preliminaries are performed. All clinical trial from phase I to phase IV are performed. The new drug registration is applied only after the completion of clinical trials. The information regarding the clinical trial as well as prescription, samples and testing protocols, product monograph, labels, and cartons must also be submitted. The application can be reviewed by DCGI in a Range of about 12-18 months.

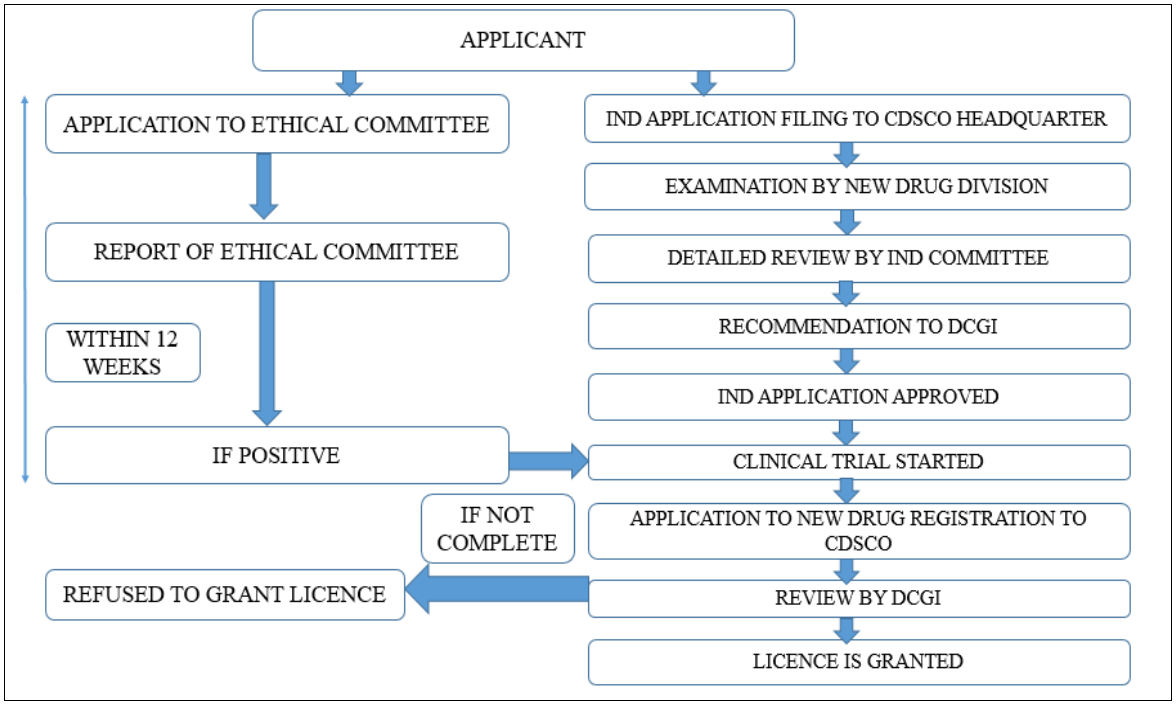

Figure 1. Drug approval procedure in India

3. Drug Approval Process in United States (10, 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 FDA is responsible for promoting and protecting public health. FDA's new drug approval process is accomplished in two phases: Clinical Trials (CT) and New Drug Application (NDA) approval. The new drug product is controlled through a new drug application (NDA). Currently such applications are accepted for review in eCTD format. The major concern about NDA is that the product shall be safety and effective. Only after submission of investigational new drug (IND) application FDA approval process begins. The US Drug Law and Regulations United States Pharmacopoeia (USP) were started in 1820 to set standards for strength and purity of drugs. Major milestones in the evolution of US drug law are:

- Food and Drugs Act (1906): It requires that the drugs must meet official standards of strength and purity.
- Federal Food, Drug and Cosmetic Act (1938): It was enacted after sulfanilamide tragedy, to prove the safety of a drug before being marketed.
- Kefauver- Harris Amendment (1962): It was passed after the thalidomide disaster. It requires the manufacturers to prove that drug is safe and effective. All the firms should send adverse effect reports to FDA.
- Orphan Drug Act (1973): This allows tax deductions for drug companies to develop orphan drugs.
- Generic drug enforcement Act (1992): It deals with convictions related to ANDA approvals.
- FDA Modernization Act (1997): It contains some changes in Federal Food, Drug and Cosmetic Act regarding collection and assessment of user fees and accelerated approval processes.

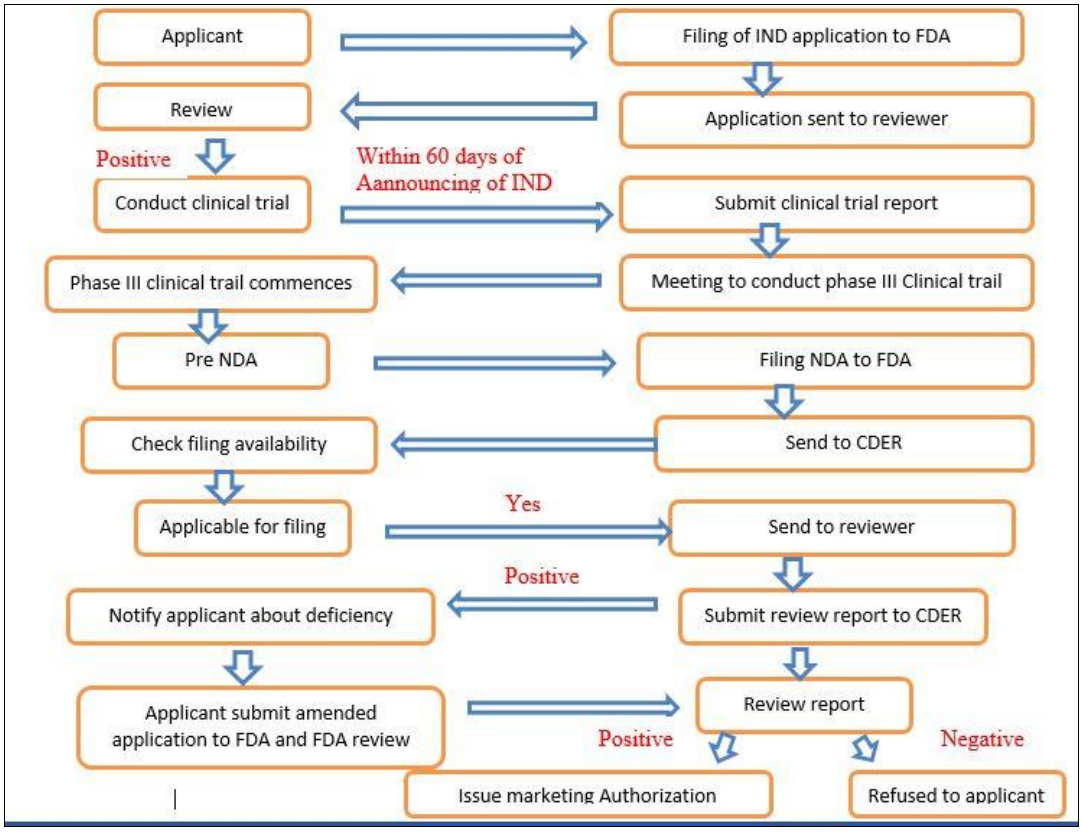

Figure 2. Drug Approval process in USA

4. Drug Approval Process in Europe (10, 12)

Before a drug is approved and to market in the European Union it goes through two regulatory steps i.e. clinical trial application and marketing authorization application which is Similar to the US requirements. In the European Union (as of July, 2013) there are 28 member states. The marketing authorization applications are approved at both the member state and centralized levels, whereas Clinical Trial Applications are approved at the member state level.

A sponsor has several options when seeking approval to market a new drug in Europe: a Centralized procedure, Mutual recognition procedure, nationalized procedure, a Decentralized procedure.

Centralized procedure

The European Medicines Agency (EMA) is a decentralized body of the EU, with headquarters in London, England. European drug approvals are overseen by the EMA. It is liable for the logical assessment of uses for approval to advertise therapeutic items in Europe (by means of the brought together strategy).

Marketing applications for drugs for use in people are assessed by the Committee for Medicinal Products for Human Use (CHMP).

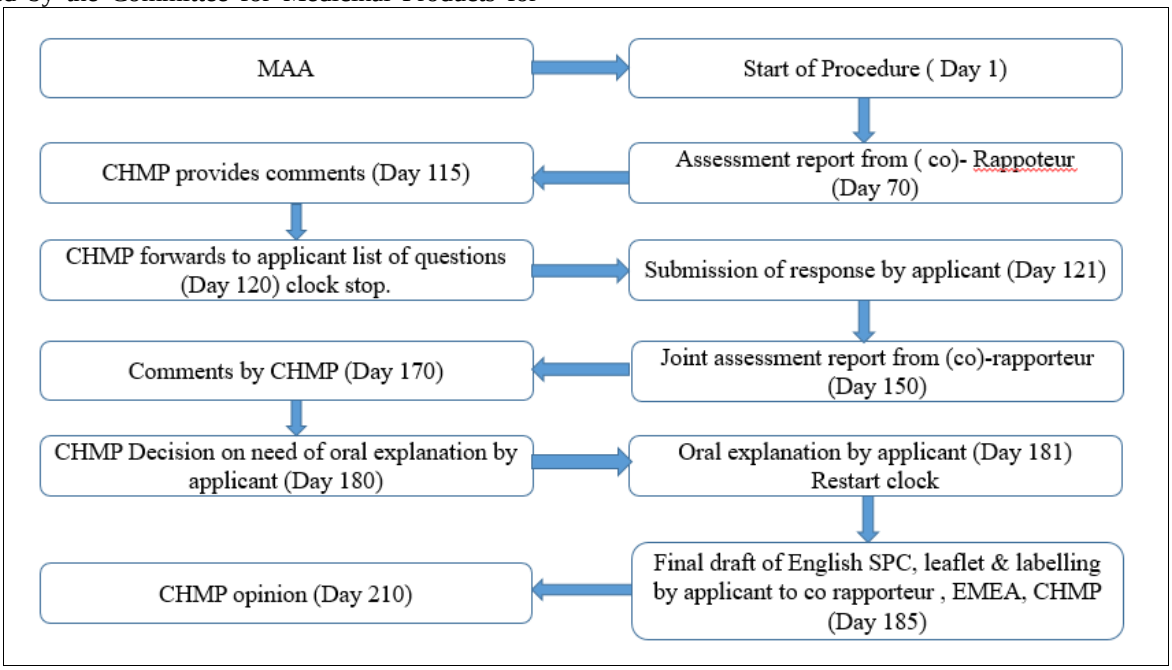

Figure 3. Centralized procedure

The centralized procedure is one which permits candidates to get a promoting approval that is legitimate all through the EU.

- Results in a solitary approval substantial in EU, Norway, Iceland and Liechtenstein.
- Application assessed by an allocated Rapporteur.
- Timeline: EMA sentiment gave inside 210 days, and submitted to European Commission for final approval.

Products that are qualified for audit under the centralized procedure must meet the accompanying rules:

- biologic drugs created by recombinant innovation, controlled articulation of qualities coding for organically dynamic proteins in prokaryotes and eukaryotes including changed mammalian cells, and hybridoma and monoclonal counter acting agent techniques
- medicinal items containing new dynamic substances for the accompanying signs: AIDS, malignant growth, neurodegenerative disarranges, diabetes, immune system sicknesses and safe dysfunctions, and viral illnesses
- orphan restorative items

Pre-submission process: At least seven months prior to submitting a marketing authorization application (MAA), a sponsor must notify the EMA of their intention to submit and the month of submission. The EMA will consider the pre submission and notify the sponsor to its decision regarding acceptance or rejection of the MAA.

Selection of rapporteur/co-rapporteur: In the EU, the rapporteur is a country-specific regulatory authority. The rapporteur (reviewer) and co-rapporteur (if needed) are identified from the CHMP members. The selection of the rapporteur of EU is based on different objective criteria, to ensure objective scientific opinion and the best use of available expertise at the EMA. The role of the rapporteur is to perform the scientific evaluation and prepare an assessment report to the CHMP in which the CHMP provides a comment. If a co-rapporteur is involved, the co-rapporteur will prepare an independent joint assessment report. The process for assigning the rapporteur/co-rapporteur is usually initiated at the CHMP meeting following the receipt of a letter of an intention to submit. The sponsor is notified of the rapporteur/co-rapporteur once the EMA has deemed a submission admissible.

Product naming: A sponsor's name for the drug product should be the same in all countries within the EU, except where it violates trademark rules. The sponsor should submit the proposed name in advance (usually four to six months, and not more than 12 months) of the marketing authorization application.

Mutual Recognition Procedure

The Mutual Recognition procedure permits candidates to acquire an advertising approval in the Concerned member states (CMS) other than the Reference member states (RMS), where the medication is recently endorsed.

- Generic industry essentially utilizes this kind of medication endorsement method.
- The Mutual Recognition Procedure is expressed in Council Directive 93/39/EEC.
- Applicant submits indistinguishable dossier to all EU part states in which they need showcasing approval, including required data.
- In pith, when a medication is affirmed for promoting approval by one Member State, it is

qualified to apply for advertising approval in other Member States through the common acknowledgment method set up since 1998.

- Identical applications are submitted to those Member States where promoting approvals are looked for.
- As soon as one part state chooses to assess the therapeutic item (so, all things considered it turns into the "RMS"), it advises this choice to other Member States (which at that point become the "CMS"), to whom applications have likewise been submitted. Concerned Member States may suspend their own assessments to anticipate evaluation by the Reference Member State.
- The choice of the Reference Member State is sent to the Concerned Member States.
- If the Concerned Member States dismiss shared acknowledgment, the issue is alluded to the CHMP of the EMA for mediation.
- The EMA advances its supposition to the European Commission, which settles on an official conclusion Altogether, the decision process may take up to 300 days if there is no objection, and 600 days when objections are raised.

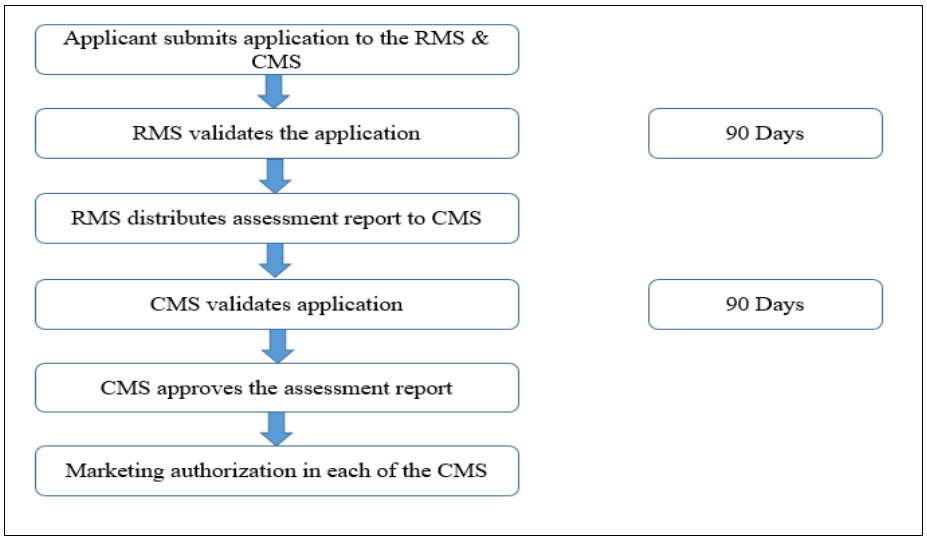

Figure 4. Mutual Recognition Procedure

Nationalized Procedure

The Nationalized technique is one which permits candidates to get a promoting approval in one part state as it were.

- In request to acquire a national advertising approval, an application must be submitted to the capable authority of the Member State.
- New dynamic substances which are not obligatory under Centralized methodology can get showcasing approval under this technique.
- Timeline for this technique is 210 Days

Decentralized procedure

Utilizing this method, organizations may apply for approval all the while in more than one EU nation for items that have not yet been approved in any EU nation and basically don't fall inside the concentrated technique's fundamental medications list.

- The candidate ought to send an application to the equipped specialists of every one of the Member States, where there is plan to acquire a promoting approval.
- The candidate may assign a nation to go about as the Reference Member State (RMS).
- The RMS will begin the strategy after the application is resolved to be finished by both the RMS and all the CMS(s).
- The RMS advances a primer Assessment Report on the dossier to the CMS(s) and the candidate inside 70 days.
- The CMS(s) is approached to give remarks on the proposed national solution status and to illuminate the RMS.
- On day 105, the RMS will advance all remarks to the candidate and stops the clock if important, until the candidate readies a reaction report.
- The RMS readies a Draft Assessment Report on day 120 and may close the system if an accord has been reached between the CMS(s) and the RMS.
- Otherwise, the CMS(s) has 90 additional days to favor the Draft Assessment Report, and different records.

5. Drug Approval Process in Canada

Health Canada’s Therapeutic Products Directorate (TPD) controls pharmaceutical medications (remedy and non-solution) and clinical gadgets for human use.

Wellbeing Canada's Therapeutic Products Directorate (TPD) regulates pharmaceutical medications (solution and nonprescription) and clinical gadgets for human use. Wellbeing Canada's Biologics and Genetic Therapies Directorate (BGTD) is answerable for managing biologics ,counting blood and blood items, viral and bacterial immunizations, cells, tissues, organs and xenografts.

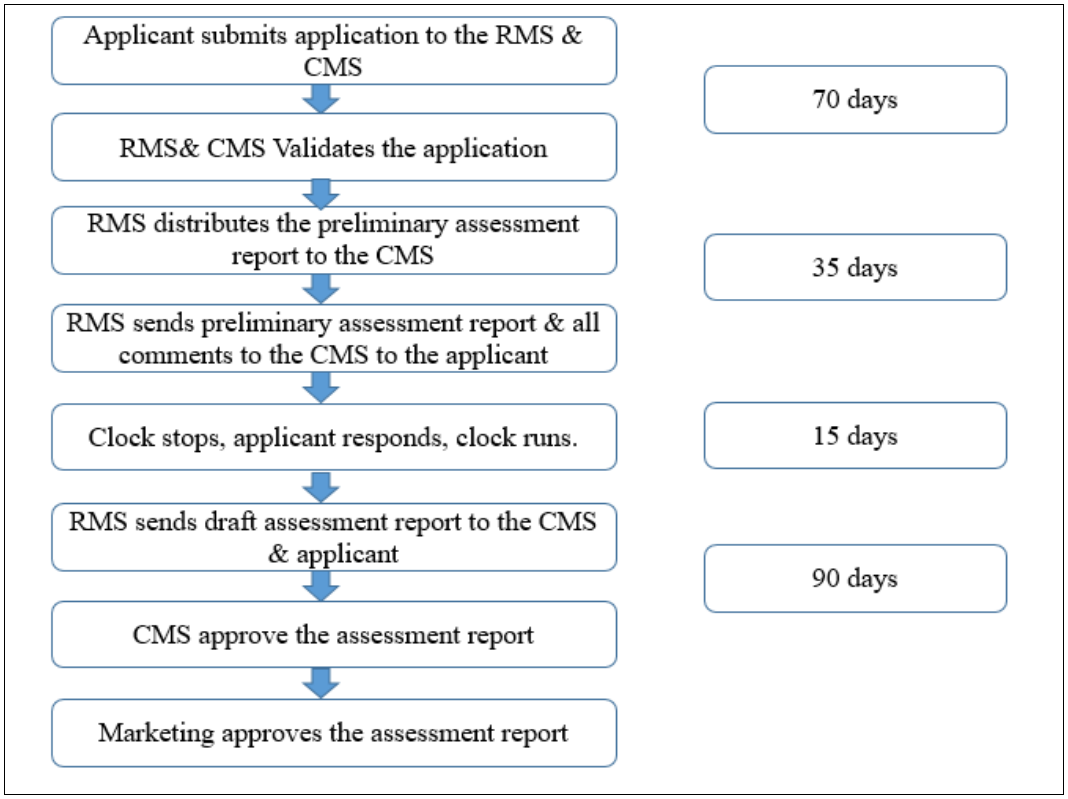

Figure 5. Decentralized procedure

Terms

Notice of Deficiency (NOD): the audit can't proceed because of insufficiencies in record

Notice of Deficiency: Withdrawal (NOD/w): if the reaction to a NOD is lacking, the TPD will give a NOD/w letter, showing the organization must pull back the accommodation.

Notice of Non-consistence (NON): shows the survey is finished and the accommodation is lacking or inadequate.

Notice of Non-consistence: Withdrawal (NON/w): if the reaction to a NON is insufficient, the organization must pull back the accommodation.

Notice of Compliance (NOC): when the sum total of what issues have been settled, the TPD will give a NOC. On the off chance that Health Canada isn't fulfilled that the sum total of what issues have been fulfilled, the TPD will give either a NOD/w or NON/w.

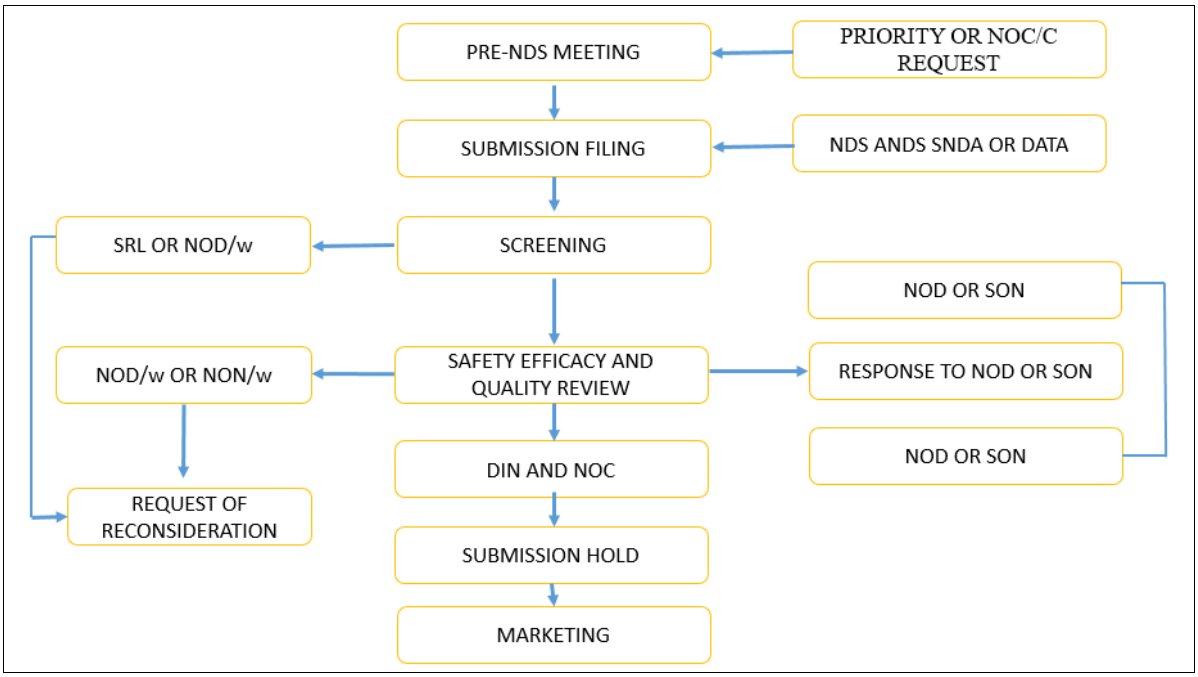

Figure 6. Drug approval process in Canada

Table 2. Comparative study of different countries

Requirements	India	U.S.	Europe	Canada
Agency	Central Drug Standard Control Organization (CDSCO)	United State Food and Drug Administration (USFDA)	European Medicines Agency (EMEA	Health Canada
Type of application		Abbreviated new drug application (ANDA)	Marketing authorisation Application.	New drug submission (NDS)
Registration Process	One Registration Process	One Registration Process	Multiple Registration Process 1. Centralized procedure 2. Mutual Recognition (At least 2 member states) 3. National procedure 4. Decentralized procedure (At least 2 member states)	One Registration Process
TSE/BSE Study data	Study data required	Study data not required	Study data required	
Post approval changes	post approval changes 1.Major 2.Moderate	Post variation in the approved drug: 1.Type IA 2.Type IB 3.Type II	Post approval changes in the approved drug: 1.Minor 2.Moderate 3.Major	

6. Conclusion

The generic drug market share is continuously increasing in most of the countries. Nowadays, the generic drugs are now becoming the strong competitors to the branded drugs. The number of generic drug approval is continuously increasing year by year, due to their low cost and effective action equivalent to branded drugs. From the above information, India, Europe, US have different drug approval process. Different countries have different regulatory procedures. So, the regulatory Affairs is field which protect public health by conducting clinical trial, ensuring product safety and efficacy.

Acknowledgements

I would like to express my gratitude to International Journal of Drug Regulatory Affairs who gave me the opportunity to publish the article.

Financial Disclosure statement: The author received no specific funding for this work.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Kumar BJ. Overview of Drug Regulatory Affairs and Regulatory Profession. International Journal of Drug Regulatory Affairs. 2013; 1 (1):1-4.
2. Harsha Y, Reddy Vs, Mary D, Nagarjunareddy D, Nagabhusanam Bb. International Journal of Pharmaceutical Research and Bio-Science. 2017; 6 (2): 170-77.
3. D.K. Sanghi, Rakesh Tiwle. Role of regulatory affairs in a pharmaceutical industry, International Journal of Pharmacy Research & Review. 2014; 4(2): 127-31.
4. Lale S, Kendre A, Gandhi M and Dani S. Role of Drug Regulatory Affairs in Pharma Industry. World Journal of Pharmaceutical Research. 2015; 4 (6): 615-25.
5. Monappa R. Sutar, Deepali R. Gawhane, C.R.Tenpe. Study of Drug Regulatory Approval Process and Comparative Requirement of Common Technical Documents (CTD) in Europe, USA and India in Coordination with Drug Developmental Process. International Journal of Pharmaceutical Sciences Review and Research. 2013; 20(2): 68-79.
6. Prajapati V, Goswami R, Makvana P, Badjatya JK. A review on drug approval process for US, Europe and India. Int J Drug Reg Affairs [Internet]. 2014 Mar 6 [cited 2020 Jun 22]; 2(1):1-11. Available from: http://ijdra.com/index.php/journal/article/view/7
7. Mahapatra AK, Sameeraja NH, Murthy PN. Drug Approval Process in United States of America, European Union and India: A Review. Applied Clinical Research, Clinical Trials and Regulatory Affairs. 2014; 1(1): 13-22.
8. Ng R. Drugs: from discovery to approval. John Wiley & Sons; 2015.p.201-202
9. Berry IR, Martin RP, editors. The pharmaceutical regulatory process. Informa healthcare; 2008. p.45.
10. Sawant AM, Mali DP, Bhagwat DA. Regulatory Requirements and Drug Approval Process in India, Europe and US. Pharmaceutical Regulatory Affairrs. 2018: 7(2): 1-10.
11. Chakraborty K, Yadav K. Drug approval process in US, Europe and India and its regulatory requirements: A Review. International Journal of Drug Regulatory Affairs (IJDRA). 2018; 6(3):31-9.
12. Mulaje SS. Mulaje S. procedure for drug approval in different countries : A Review. JDDT [Internet]. 17 Mar. 2013 [cited 22 Jun. 2020]; 3(2). Available from: http://jddtonline.info/index.php/jddt/article/view/409