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REVIEW ON: PHARMACEUTICAL DRUG REGULATORY AFFAIRS & REGULATORY REQUIREMENT FOR DRUG'S APPROVAL IN INDIA, US & EUROPE MARKET

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ABSTRACT

A Drug regulatory approval process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. Drug Regulatory affairs (DRA) is a dynamic, rewarding field that includes both scientific and legal aspects of drug development. DRA department involved in critical roles in a pharmaceutical industry because it is concern about the healthcare product lifecycle, provide strategic, tactical and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world. All Countries have their own regulatory authority, which play role in for enforcing the rules and regulations and issue the guidelines to regulate drug development process, licensing, registration, manufacturing, marketing, labeling and the product life cycle of pharmaceutical products. The approval time in all the countries is almost the same 12 to 18 months with their different approval charges. In this article we focus on the Drug Regulatory affairs, drug approval process and regulatory requirements according to Central Drug Standard Control Organization (CDSCO), US Food & Drug Administration (USFDA), and EMEA, CHMP & NATIONAL HEALTH AGENCY.

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INTRODUCTION [1-3]

All substances have poisonous nature beyond a certain dose. The right dose differentiates whether the substance is poison or remedy. As per Paracelsus, "even no drug product is completely safe or efficacious in all circumstances, but there is a moral as well as legal, expectation that appropriate steps are taken to assure optimal quality, safety and efficacy by the producers concerned".

Every Pharmaceutical companies have follow Good Manufacturing Practices which produced products with Safety, Identity, Strength, Purity & Quality; in current scenarios The Regulatory Affairs Profession believe the New Approach to regulation will eventually be adopted for all healthcare products as it represents the best model for delivering new healthcare advances to market in a reasonable time with acceptable safety. Regulatory Affairs (RA) or Drug Regulatory Affairs (DRA) is a profession within regulated industries, such as pharmaceuticals, medical devices. Regulatory Affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, Biologics and functional foods) most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs professionals. Regulatory bodies provide strategic, tactical and operational direction and support for working within regulations to expedite the development and delivery of safe and effective healthcare products to individuals around the world.

Every country has its own regulatory agencies which are holding the all the regulatory matters of that country relating to the drug substances, known as Regulatory authorities or agencies, which act as a guardian that ensures the safety, efficacy and quality of drugs available to the public, to identify the strengths and weaknesses of drug regulation and to propose strategies to improve drug regulation. Each regulatory system had faced certain circumstances which led to current well-defined controlled regulatory framework. This has resulted into systematic manufacturing and marketing of safe, efficacious and qualitative drugs. With the growth of industry, the legislations from each region have become more and more complex and created a need for regulatory professional. The Regulation of drug approval can explained as (FIGURE-1).

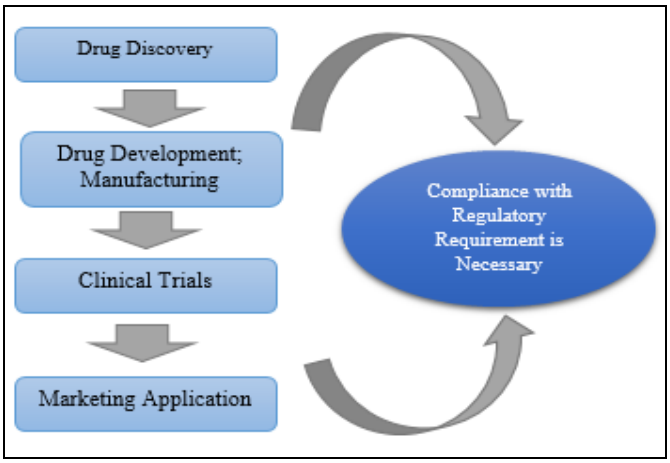

FIGURE 1: The Regulation of Drug Approval Process.

HISTORICAL BACKGROUND OF DRUG REGULATORY AFFAIRS

During the 20th century there were no laws & regulations to protect the public health from the unwanted harmful effects. Hence result in 1950's, multiple tragedies such as the sulfanilamide elixir, vaccine tragedy, the Ginger Jake poisoning and thalidomide tragedy, led to a substantial increase of the legislations for drug products quality, safety, identity, strength and efficacy. This has also resulted into stricter norms for marketing authorization and Good Manufacturing Practices (GMP). In 1937 due to diethylene glycol poisoning, 100 people died and in 1956 in West Germany a thalidomide disaster which majorly triggered for the development of the modern regulatory controls on the drug development and supply. Hence to ensure the quality, safety, identity, strength and efficacy of drug products and in order to assure the continued protection of public health, the regulatory agencies were introduced in the late 1950's.

OBJECTIVES OF DRUG REGULATORY AFFAIRS [5]

- Regulatory Affairs persons coordinate and document internal regulatory processes, such as cGMP, internal audits, inspections, license renewals or registrations.
- Provide suggestion to companies on the regulatory aspects and climate that would affect their proposed activities.
- They may also compile and prepare materials for submission to regulatory agencies like Drug Master Formula File.
- The regulatory bodies play a vital role in between the companies and the government agencies.
- Regulatory affairs department plays a vital role to ensure the safety and efficacy of the drugs available to the public in the market.
- Regulatory bodies involves in creating guidelines for clinical and non-clinical area, like the manufacturing, importation, distribution of drugs and also monitors adverse drug reactions.
- Regulatory affairs help in the legalization covering all products with a medicinal claim and all relevant pharmaceutical activities, whether carried out by the public or the private sector.

REGULATORY BODIES IN THE WORLD

Many country has its own regulatory agencies which works for the all the regulatory matters of that country relating to the drug substances & countries include various sub-coordinating bodies in order to achieve the effective functioning of the implemented guidelines. These various agencies shown in TABLE-1.

TABLE 1: Different Regulatory Bodies in the World.

COUNTRIES	REGULATING BODIES
Australia	Therapeutic Goods Administration (TGA)
Brazil	Agencia Nacional de Vigiloncia Sanitaria (ANVISA)
Canada	Health Canada
China	State Food and Drug Administration
Costa Rica	Ministry of Health
Denmark	Danish Medicines Agency
Europe	European Medicines Agency (EMEA)
Germany	Federal Institute of Drugs and Medical Devices
India	Central Drug Standard Control Organization (CDSCO)
Italy	Italian Medicines Agency (AIFA)
Ireland	Italian Medicines Agency (AIFA)
Japan	Ministry of Health, Labour and Welfare (MHLW)
Malaysia	National Pharmaceutical Control Bureau
New Zealand	Med Safe - Medicines and Medical Devices Safety Authority
Netherlands	Medicines Evaluation Board
Nigeria	National Agency for Food and Drug Administration and Control (NAFDAC)
Pakistan	Drug Control Organization, Ministry of Health.
Singapore	Centre for Pharmaceutical Administration Health Sciences Authority
South Africa	Medicines Control Council (MCC), South African Health Products Regulatory Authority (SAHPRA)
Switzerland	Swissmedic, Swiss Agency for Therapeutic Products
Thailand	Thailand Food and Drug Administration
Uganda	Uganda National Council for Science and Technology (UNCST)
USA	Food and Drug Administration (FDA)
United Kingdom	Medicines and Healthcare Products Regulatory Agency (MHRA)
Germany	Federal Institute of health and Medical Devices
Sri Lanka	Cosmetics, Devices & Drugs regulatory authority of Sir Lanka
Uganda	Uganda National Council for Science and Technology (UNCST)
Ukraine	Ministry of Health
Regulating Authorities of Gulf Countries	
State of Qatar	Pharmacy and Drug Control Department
Saudi Arabia	Saudi Food and drug Authority
United Arab Emirates (UAE)	Registration and Drug Control Department
Bahrain	Pharmacy and Drug Control Department
State of Kuwait	Pharmaceutical and Herbal Medicines Registration and Control Administration, Kuwait Drug and Food
State of Oman	General Directorate of Pharmacy and Drug Control

International Regulating Bodies

Several countries don't have their own regulating bodies or the improperly regulated agencies so they follow the global guidelines. The majority of the Gulf countries don't have their own regulatory bodies, some of the countries such as Iran, Israel, Iraq, Jordan, Kuwait, Oman, Palestine, Qatar, Saudi Arabia, Syria etc., so they adopt the most suitable guidelines according to their region (TABLE-2).

TABLE 2: International Regulating Bodies.

Regulating Body	Headquarters
World Health Organization (WHO)	Geneva, Switzerland
World Trade Organization (WTO)	Geneva, Switzerland
International Council on Harmonization (ICH)	Geneva, Switzerland
Pan American Health Organization (PAHO)	Washington, D.C., United State
World Intellectual Property Organization (WIPO)	Geneva, Switzerland

SCOPES OF DRUG REGULATORY AFFAIRS IN PHARMACEUTICAL INDUSTRY

DRAs professionals give strategic and technical advice to R&D, Production, Quality department and Many more, right from the development of a product, making an important contribution both commercially and scientifically to the success of a development program and company as a whole (FIGURE-2).

FIGURE 2: Areas covered by Drug Regulatory Affairs.

RAs professionals play vital role in industry, government regulatory authorities and academics. The wide range of regulatory professionals includes in these areas: Pharmaceuticals, Medical devices, In vitro diagnostics, Biologics and biotechnology, Nutritional Products, Cosmetics and Veterinary Products.

New drug application (NDA) is an application submitted to the respective regulatory authority for permission to market a new drug. After NDA received by the agency, it undergoes a technical screening. 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: (FIGURE-3)

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

TYPES & SUMMARY OF CLINICAL TRIALS

TYPES	PHASE I	PHASE II	PHASE III	PHASE IV
OBJECTIVES:	Determine the metabolic and pharmacological actions and the maximally tolerated dose	Evaluate effectiveness, determine the short-term side effects and identify common risks for a specific population and disease	Obtain additional information about the effectiveness on clinical outcomes and evaluate the overall risk-benefit ratio in a demographically diverse sample	Monitor ongoing safety in large populations and identify additional uses of the agent that might be approved by the FDA
FACTORS TO BE IDENTIFIED:	-Bioavailability -Bioequivalence -Dose proportionality -Metabolism -Pharmacodynamics -Pharmacokinetics	-Bioavailability -Drug-disease interactions -Drug-drug interactions -Efficacy at various doses -Pharmakodynamics -Pharmakokinetics -Patient safety	-Drug-disease interactions -Drug-drug interactions -Dosage intervals -Risk-benefit information -Efficacy and safety for subgroups	-Epidemiological data -Efficacy and safety within large, diverse populations -Pharmacoeconomics
DATA FOCUS:	-Vital signs -Plasma and serum levels -Adverse events	-Dose response and tolerance -Adverse events -Efficacy	-Laboratory data -Efficacy -Adverse events	-Efficacy -Pharmacoeconomics -Epidemiology -Adverse events
DESIGN FEATURES:	-Single, ascending dose tiers -Unblinded -Uncontrolled	-Placebo controlled comparisons -Active controlled comparisons -Well-defined entry criteria	-Randomized -Controlled -2-3 treatment arms -Broader eligibility criteria	-Uncontrolled -Observational
DURATION:	Up to 1 month	Several months	Several years	Ongoing (following FDA approval)
POPULATION:	Healthy volunteers or individuals with the target disease (such as cancer or HIV)	Individuals with target disease	Individuals with target disease	Individuals with target disease, as well as new age groups, genders, etc.
SAMPLE SIZE:	20 to 80	200 to 300	Hundreds to thousands	Thousands

FIGURE 3: Types & Summary of Clinical Trials.

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, 7].

DRUG APPROVAL PROCESS INDIA [3, 4-6, 7, 8]

Under the current Indian legal and regulatory regime, the manufacture, sale, import, exports and clinical research of drugs and cosmetics is governed by the following laws:

1. The Drugs and Cosmetics Act, 1940
2. The Pharmacy Act, 1948
3. The Drugs and Magic Remedies (Objectionable Advertisement) Act, 1954
4. The Narcotic Drugs and Psychotropic Substances Act, 1985
5. The Medicinal and Toilet Preparations (Excise Duties) Act, 1956
6. The Drugs (Prices Control) Order 1995 (under the Essential Commodities Act.
7. The Industries (Development and Regulation) Act, 1951
8. The Trade and Merchandise Marks Act, 1958
9. The Indian Patent and Design Act, 1970
10. The Factories Act.

In India for approval of drug products they must follow the Drug & Cosmetic Act, i.e. 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. 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 mandatory information required for approval of an application to import or manufacture of new drug for marketing in India.

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. 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. For an investigational new drug, the sponsor needs to provide detailed information to the DCGI about:

1. Generic name
2. Patent status
3. Brief description of physico-chemical/biological
4. Technical information
   a) Stability
   b) Specifications
   c) Manufacturing process
   d) Worldwide regulatory status
   e) Animal pharmacology and toxicity studies
5. Published clinical trial reports
6. Proposed protocol and pro-formas
7. Trial duration
8. during master file
9. Undertaking to Report Serious or Life-threatening Adverse Drug Reactions.

- 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.

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 CDSCO (FIGURE-4).

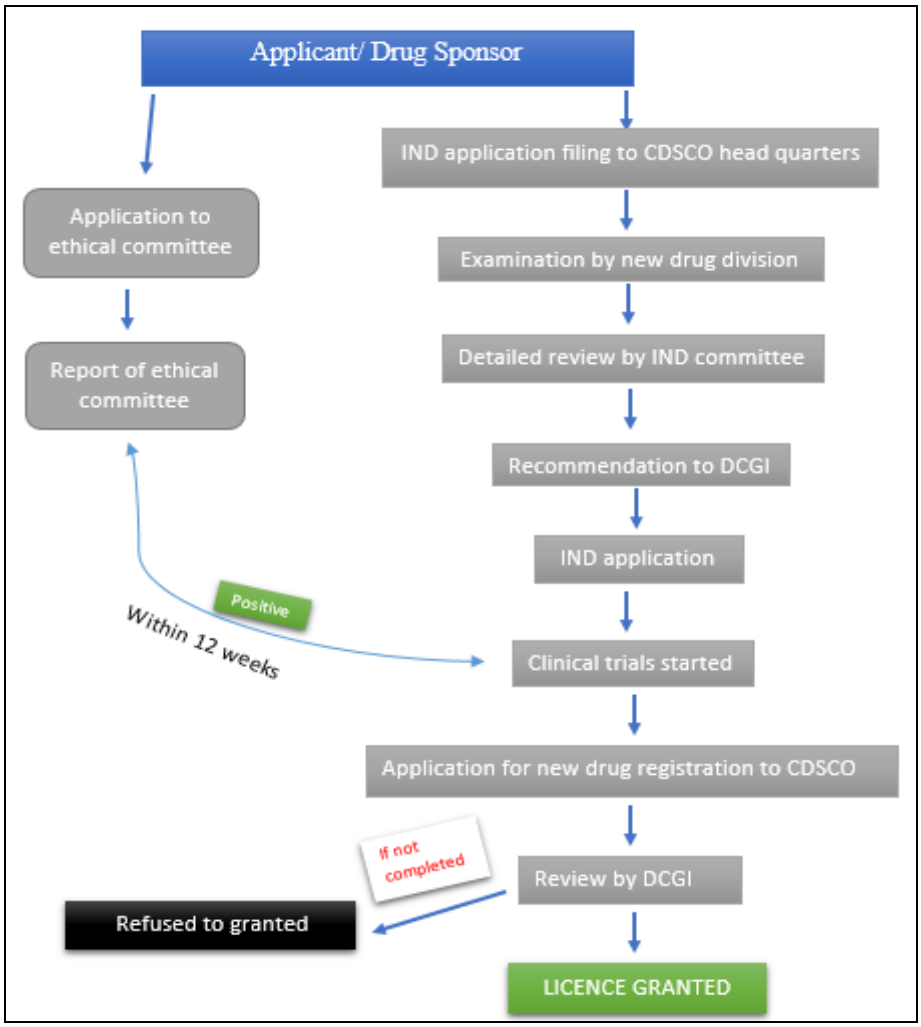

FIGURE 4: Drug Approval Process in India.

Stages of approval:
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.

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.

DRUG APPROVAL PROCESS IN UNITED STATES [5, 7, 9, 10]

The United States (US) has perhaps the world's most stringent standards for approving new drugs. Drug approval standards in the US 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.

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:

- Pure Food and Drugs Act (1906): involved prohibited the sale of misbranded or adulterated food and drugs in interstate commerce and laid a foundation for the nation's first consumer protection agency, the FDA. It requires that the drugs must meet official standards of strength and purity.
- Federal Food, Drug and Cosmetic (FFDCA, FDCA, or FD&C) Act (1938): It was enacted after sulfanilamide tragedy, to prove the safety of a drug before being marketed. It replaced the earlier Pure Food and Drug Act of 1906.
- Drug Efficacy Amendment or 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): The main focus of this is the acknowledgment in the advancement of technological, trade, and public health complexities.
- FDA Food Safety Modernization Act (2011): It contains some changes in Federal Food, Drug and Cosmetic Act regarding collection and assessment of user fees and accelerated approval processes.

Different types of application submitted to FDAs for Drug Approval these are:

Investigational New Drug (IND) Application

For US FDA issued FORM FDA 1571 for requesting the Investigational New Drug (IND) Application. It's an application filed to the FDA or CDER (Central Drug Evolution & Research) 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 Pharmacological & Toxicological testing data of the drug in humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed.

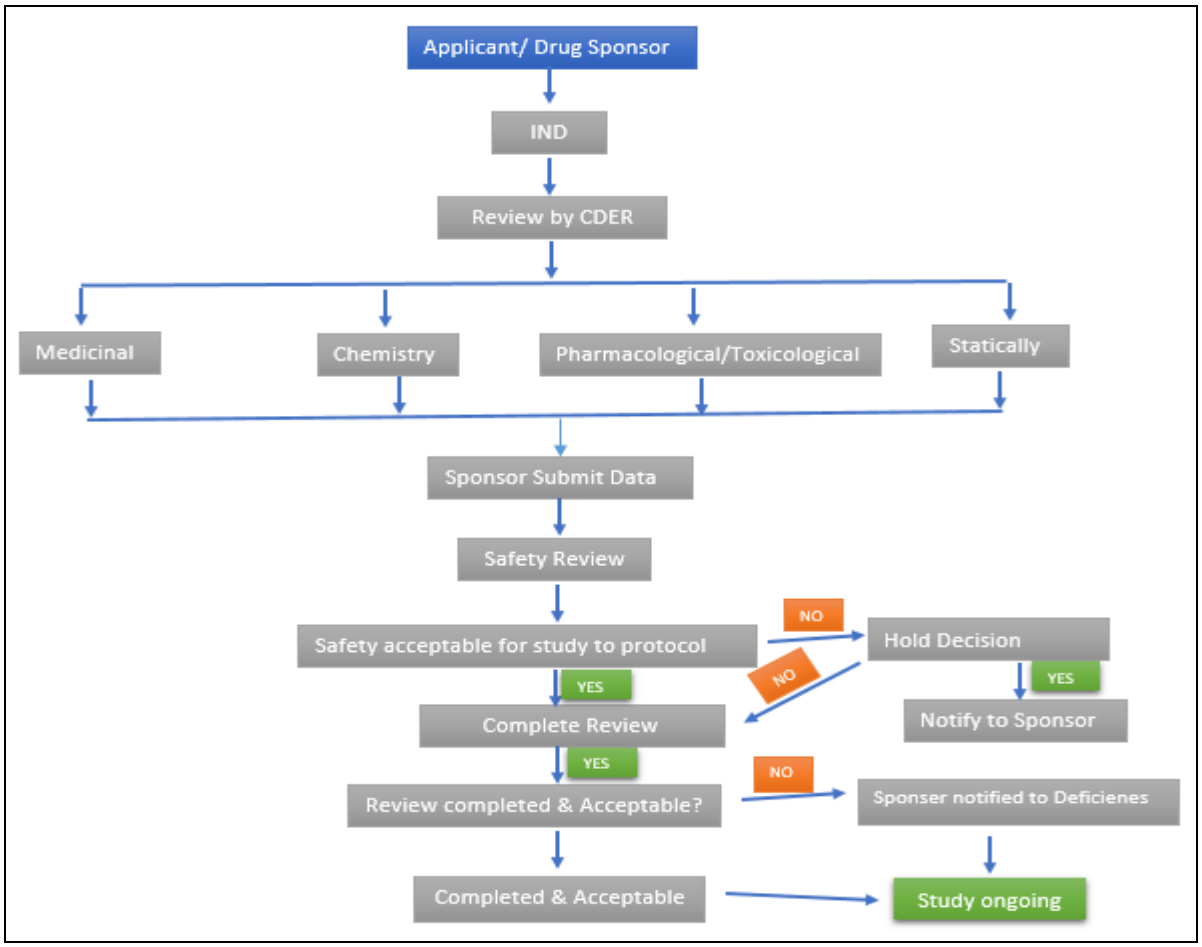

FIGURE 5: Investigational New Drug (IND) Application.

The requirements for the content and format of IND application are given in the 21 Code of Federal Regulations (CFR), Section 312. A sponsor (commercial organization) or an investigator who intends to conduct a clinical investigation should submit an "Investigational New Drug Application" in the following order (FIGURE-5):

1. Form FDA 1571,
2. Table of contents,
3. Introductory statement and investigational plan,
4. Investigator's brochure,
5. Protocols,
6. Chemistry, manufacturing and control (CMC) information,
7. Pharmacology and toxicology information,
8. Previous human experience,
9. Additional information.

New drug application (NDA)

A new drug application (NDA) filed for marketing of Drug in US & considered to be in Phase IV trials; 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 NDA, the actual request to manufacture and sell the drug in the United States. Generally approval of an NDA is granted within two years (on an average), however, this process can be completed from 60 Days & More. In this phase, new areas, uses or new populations, long-term effects, and how participants respond to different dosages are explored (FIGURE-6).

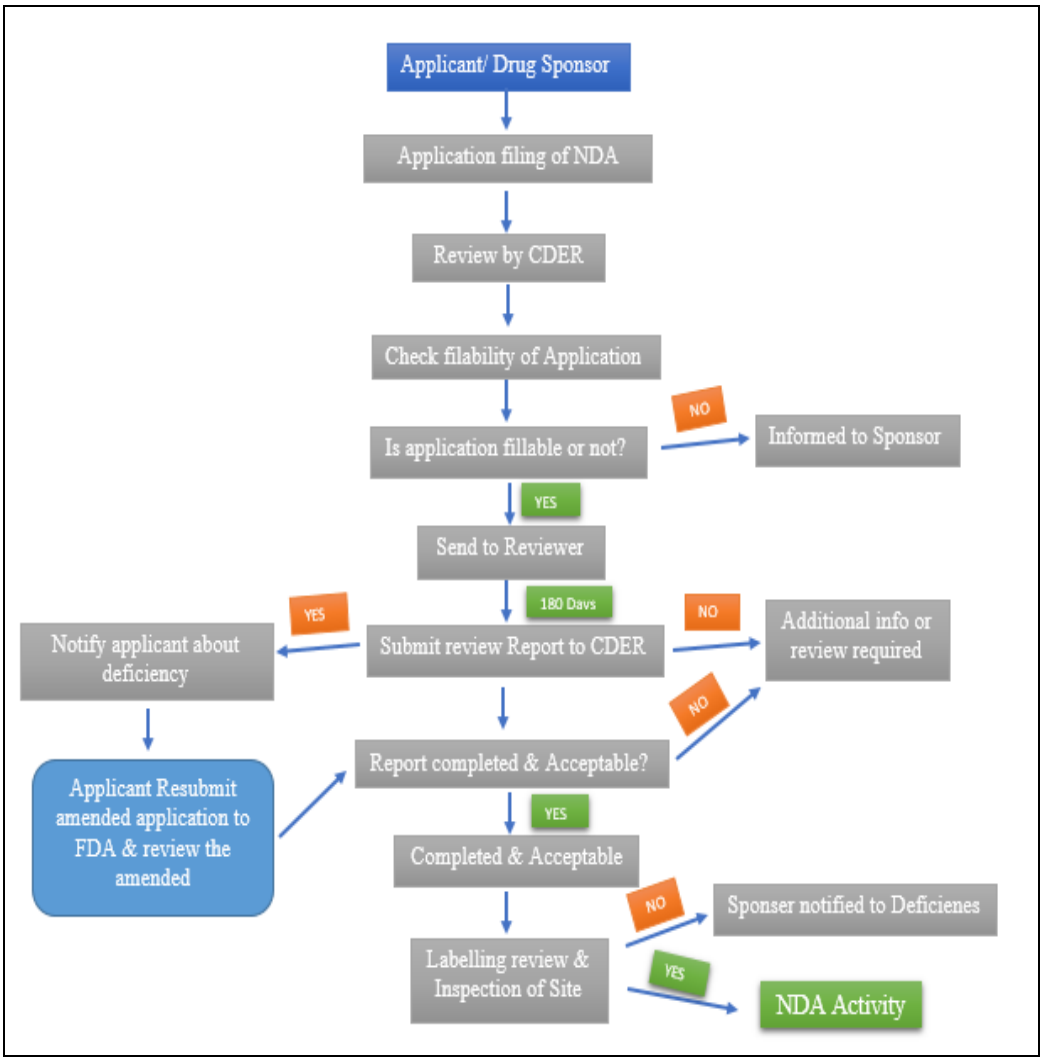

FIGURE 6: New drug application (NDA).

Contents and Format of NDA, Two copies of the application are: (1) Archival & (2) 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:
   a) Application form FDA 356
   b) Index
   c) Summary
   d) Technical sections: further following types
      i. Chemistry, manufacturing and controls section
      ii. Non-clinical pharmacology and toxicology section
      iii. Human pharmacokinetics and bioavailability section
      iv. Microbiology section
      v. Clinical data section
      vi. Statistical section
      vii. Pediatric use section
   e) Samples and Labeling
   f) Case report forms

B. Review Copy: Each technical section is separately bound in each folder. Each technical sect ion should contain:
   a) Index
   b) Copy of FDA Form 356 h
   c) Copy of cover letter
   d) Letters of authorization
   e) Copy of application summary

Abbreviated New Drug Application (ANDA)

An abbreviated new drug application (ANDA) is applied for products with same or closely related active ingredients, dosage form, and strength, route of administration, use and labeling as product already shown to be safe and effective. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. It is used when the patent has expired for a product, and a company wants to market its copy. ANDA submitted to CDER, Office of Generic Drugs, where it is reviewed and approved; once approved, an applicant may manufacture and market the generic drug product to provide a safe, effective, lower cost alternative to the brand-name drug it references. Content and Format of ANDA is-

A. Application form
B. Table of contents
C. Basis for ANDA submission
D. Conditions of use.

Biologics License Application (BLA)

The biologics license application is a request for permission to introduce, or deliver for introduction, a biologic product into interstate commerce (21 CFR 601.2). The BLA is regulated under 21 CFR 600 – 680. A BLA is submitted by any legal person or entity who is engaged in manufacture or an applicant for a license who takes responsibility for compliance with product and establishment standards. Form 356h specifies the requirements for a BLA. This includes: Applicant information, Product/manufacturing information, Pre-clinical studies, Clinical studies, Labeling. A BLA is submitted after an investigational new drug has been approved. If the Form 356h is missing information, the FDA will reply within 74 days. A BLA asserts that the product is "safe, pure, and potent", the manufacturing facilities are inspect able, and each package of the product bears the license number.

DRUG APPROVAL PROCESS IN EUROPE [5-7, 11, 12-14]

In European Union (EU), the medical products were approved for marketing at the National level initially. The European Medicines Evaluation Agency (EMEA) was established in London, in the year 1995, to coordinate the EU member states for evaluating and supervising the medicinal products for both human and veterinary use. European Union consists of 28 Member states. Similarly, the drug approval process in European countries is also completed in two phases: clinical trial applications (CTA) and marketing authorization application (MAA).

A CTA is filed to the competent authority of the state to conduct the clinical trial within EU. 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. After completing the phases of clinical trial, MAA is filed including all animal and human data, its analyses, as well as pharmacokinetics, manufacturing and proposed labelling.

The European Legislation containing the pharmaceutical directives has been published in the following volumes entitled The Rules Governing Medicinal Products in the European Union.

Volume 1: Pharmaceutical Legislation for Medicinal Products for human use.
Volume 2: Notice to Applicants & Regulatory guidelines for Medicinal Products for human use.
Volume 3: Scientific Guidelines for Medicinal Products for human use.
Volume 4: GMP Guidelines for Medicinal Products for human and veterinary use.
Volume 5: Pharmaceutical Legislation for Medicinal Products for veterinary use.
Volume 6: Notice to Applicants & Regulatory guidelines for Medicinal Products for veterinary use.
Volume 7: Scientific Guidelines for Medicinal Products for veterinary use.
Volume 8: Maximum Residue Limits.
Volume 9: Pharmacovigilance Guidelines for Medicinal Products for human and veterinary use.
Volume 10: Clinical Trials Guidelines.

Europe has multiple structures and administrative procedures for obtaining market authorization of pharmaceuticals. There are four different routes in the European Union to obtain marketing approval of pharmaceuticals:

Centralized Procedure

This is the centralized procedure which provides applicant the market authorization which is valid throughout the European Union. This authorization is valid in European Union, Norway, Iceland and Liechtenstein. The Committee for Human Medicinal Products (CHMP) evaluate the applications received by the Europe, the Middle East and Africa (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. 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 license is recommended, a European Public Assessment Report (EPAR) is produced and marketing authorization is issued. This authorization 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-7 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.
- Orphan medicines.

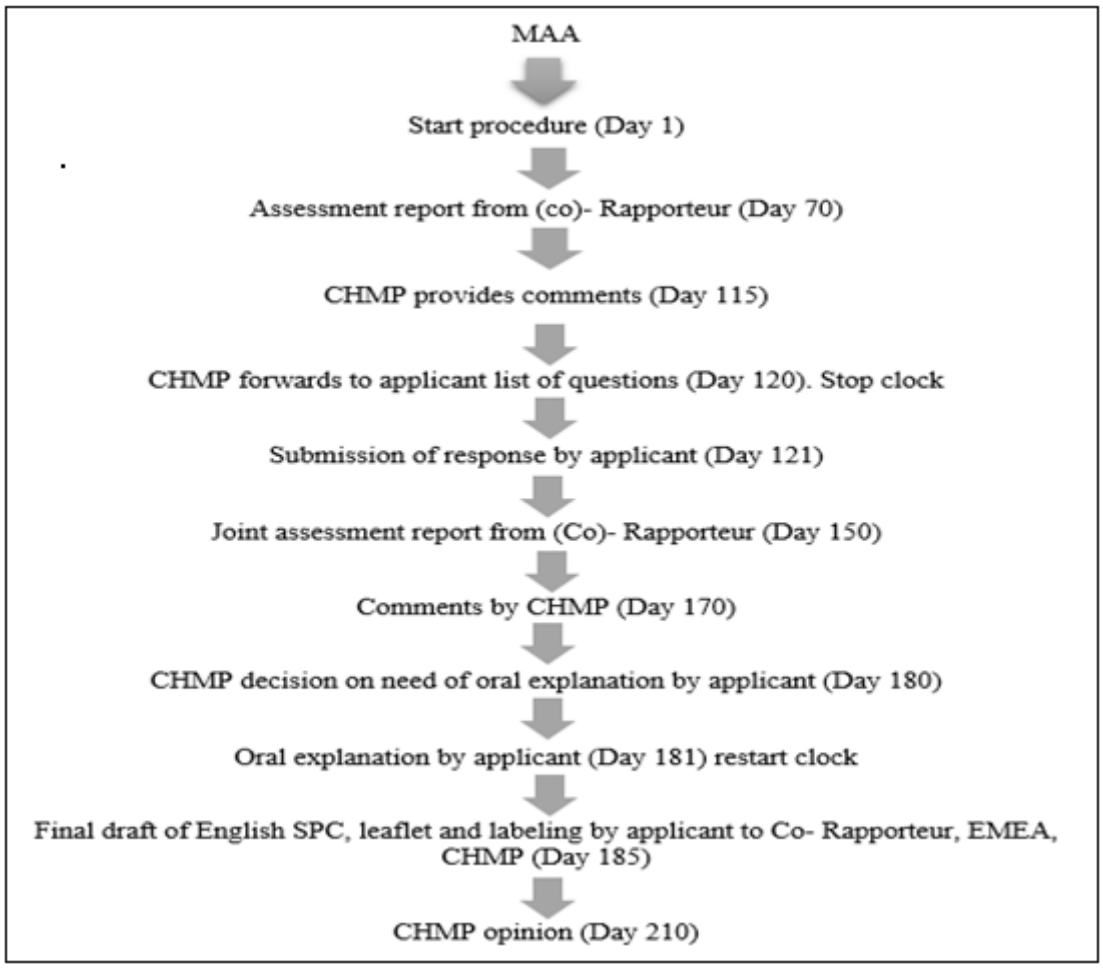

FIGURE 7: Centralized Procedure for Drug Approval in Europe.

Decentralized Procedure

In order to obtain marketing authorizations in several 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 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. 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-8 represent the decentralized procedure for marketing authorization in EU.

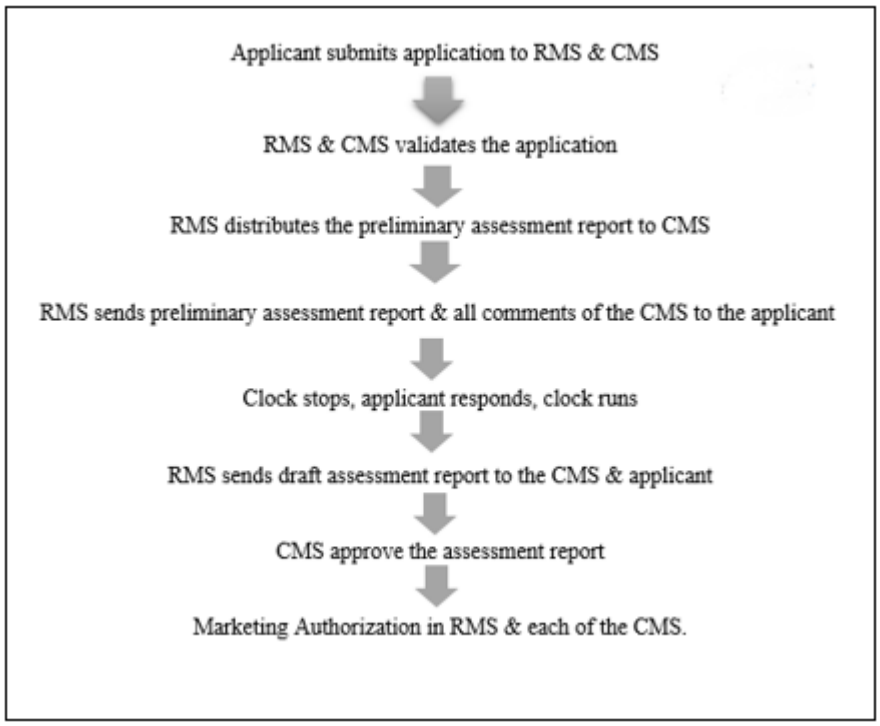

FIGURE 8: Decentralized Procedure for Drug Approval in Europe.

Under this procedure following product cannot be registered: Orphans Medicinal Product, All Biotechnology Based Product, Specified Aids and Cancer Medicines, Specified Antiviral Medicines, Specified Medicines for Neurodegenerative Disorder including diabetes and Specified Medicines for Auto immune Diseases/dysfunctions.

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. The Time periods for this whole procedure is 210 Days. FIGURE-8 represent the nationalized procedure for marketing authorization in EU.

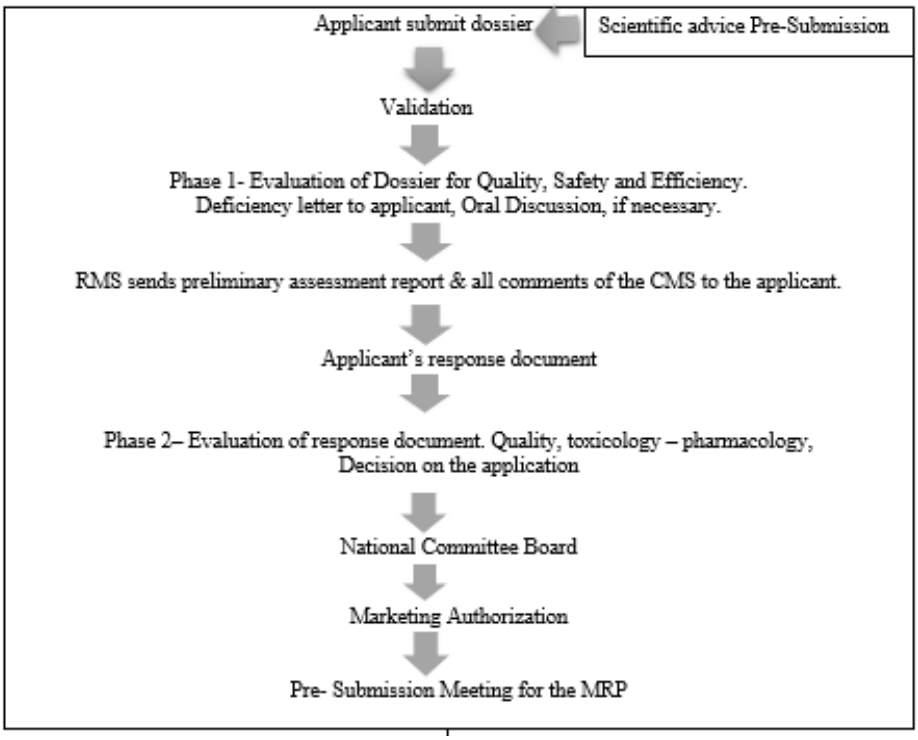

FIGURE 9: Nationalized Procedure for Drug Approval in Europe.

Under this procedure also following product cannot be registered: Orphans Medicinal Product, All Biotechnology Based Product, Specified Aids and Cancer Medicines, Specified Antiviral Medicines, Specified Medicines for Neurodegenerative Disorder including diabetes and Specified Medicines for Auto immune Diseases/dysfunctions.

Mutual Recognition Procedure (MRP)

The Mutual Recognition procedure mainly used for Generic drugs approval & allows applicants to obtain a marketing authorization in the concerned CMS other than the RMS, where the drug is previously approved. In this Procedure the 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. This process may consume a time period of 390 days. FIGURE-10 represents the mutual recognition procedure for drug approval process in EU.

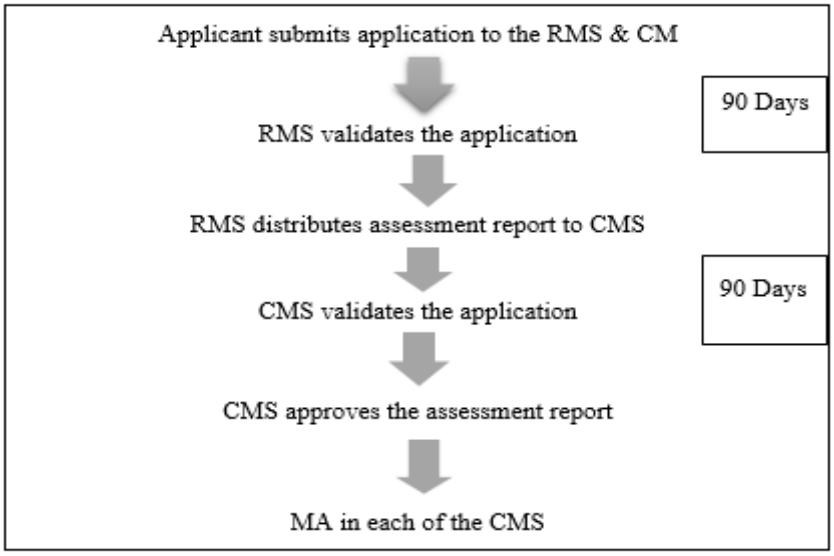

FIGURE 10: Mutual Recognition Procedure for Drug Approval in Europe.

SUMMARY

Summary of Approval of Drug in India, US & Europe Market have many difference parameter, which was summarized in TABLE-3.

TABLE 3: Difference between India, US & Europe Market's Requirements.

REGULATION DIFFERENCE BETWEEN INDIA, US & EUROPE			
Requirements	**INDIA**	**US**	**EUROPE**
Agency	One agency DCGI	One agency USFDA	Multiple agencies MEA HMP National health agencies
Registration process	1 registration process	1 registration process	Multiple registration process Centralized (European community) Cecentralized Nutual recognition National
TSE/BSE study data	Required	Not required	Required
Post approval quality changes	Two types: Major Moderate	Three types: Minor Moderate Major	Three types: Type IA variation Type IB variation Type II variation
ADMINISTRATIVE REQUIREMENTS			
Requirements	**INDIA**	**US**	**EUROPE**
Application	MAA	ANDA/NDA	MAA
Debarment classification	Not required	Required	Not required
Number of copies	1	3	1
Approval timeline	2 - 18 months	18 months	12 months
Presentation	Paper	eCTD & Paper	eCTD
3. MANUFACTURING AND CONTROL REQUIREMENTS			
Requirements	**INDIA**	**US**	**EUROPE**
Number of batches	1	1	3
Packaging	Not addressed	A minimum of 1,00,0000	Not required
Process validation	Required	Not required at the time of submission	Required
Batch size	Pilot scale batch	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

CONCLUSION

The Regulatory Affairs department is most widely covered evolving and growing and is the one which is least impacted during the acquisition and merger, and also during recession. For Mandatory fulfill of Regulatory laws some companies hires third parties or consultancy those involved in Regulatory submission. The proper implementation of regulatory guidelines and laws will improve the economic growth of the company and also improves the safety of the people. The main purpose of regulating all the Pharmaceutical products by regulatory agencies is to provide safety for public health. Regulatory agencies work is to make sure that the pharmaceutical companies comply with all, the regulations and standards, so that the patient's well-being is protected. In present time the Drug Approval Process in India, US & Europe is the most demanding in the world, in those the drug approval of US Market make most impact for Pharmaceutical companies. 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. The approval time in all the countries is almost the same i.e., 12 to 18 months. US agency have high charges for drug approval is very high in compared with EUROPE and INDIA.

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