A REVIEW ON PHARAMACEUTICAL REGULATORY AGENCIES OF INDIA, USA AND EUROPE

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***Abstract*: Drugs play a major role in saving lives, maintaining health, preventing diseases, stopping epidemics and in improving economy of a country. Therefore, people, government, pharmaceutical industries and research institutes spend money on drugs. However, in order to do so, drug must be safe, effective and of good quality. This means the development, production, importation, exportation, and distribution of drugs are regulated to ensure that they meet prescribed standards. For effective regulation of pharmaceutical products, governments establish strong National Regulatory Authorities (NRAs), to assure that medicines are regulated effectively thereby protecting and promoting public health. Pharmaceutical regulations across the globe play a vital role in guaranteeing the safety, quality and efficacy of the drugs. Pharmaceutical regulatory agency is accountable to enforce the regulations and issue guidelines for drug development, licensing, registration, producing, labelling, storage, marketing, distribution, pricing of drugs, import and post marketing studies of pharmaceutical products. Pharmaceutical industries, while pursuing an international market, must comply with pharmaceutical regulations of other countries, which have different regulatory requirements. A single regulatory approach for Marketing Authorization Application (MAA) of a drug product applicable to different countries is difficult. Therefore, Common Technical Document (CTD) was developed to provide a common format for submission of applications electronically for registration of pharmaceuticals. In this review article, an overview of pharmaceutical regulatory agencies of three countries: India, USA and Europe is covered.**

***Keywords*: Regulatory Agency, CDSCO, US FDA, EMA, Marketing Authorization Application, Common Technical Document**

INTRODUCTION:

Pharmaceutical regulations are a set of legal, administrative, and technical measures that governments implement to make sure the safety, efficacy, and quality of medicines, as well as the relevance and accuracy of product data available to the public. The term "regulation" includes a variety of texts such as guidelines, recommendations, procedures, policies, etc. that have different legal bases and authority [1]. The regulations are required for both new and pre-existing products, domestically produced products and those imported from other countries. The main aim of regulatory agencies is to maintain the standards of the drug at every step to cater for the patient population [2]. A regulatory system for medicines must provide access to effective treatments in time for patients, protect patient safety, and promote research into new treatments [3]. Regulatory agencies provide strategic, tactical and operational guidance as well as support for working within regulations to accelerate the development and delivery of safe and effective medicines or healthcare products to public. Current pharmaceutical industry is very organized, systematic and compliant to international regulations. Multiple tragedies like sulphanilamide elixir, vaccine tragedy and thalidomide tragedy led to the need for a well-controlled regulatory framework. This has resulted into efficient manufacturing and marketing of safe, effective and quality healthcare products [4].

Major National Regulatory Agencies World Wide:

Table 1: National Regulatory Agencies [4]

Country	Name of Regulatory Authority
India	Central Drug Standard Control Organization (CDSCO)
USA	Food and Drug Administration (FDA)
Europe	European Medicines Agency (EMA)
UK	Medicines and Healthcare Products Regulatory Agency (MHRA)
Australia	Therapeutic Goods Administration (TGA)
Canada	Health Canada
New Zealand	Medicines and Medical Devices Safety Authority (Medsafe)
China	State Food and Drug Administration (SFDA)
Japan	Ministry of Health, Labour & Welfare (MHLW)
Switzerland	SWISSMEDIC, Swiss Agency for Therapeutic Products

International Regulatory Agencies and Organizations:

- World Health Organization (WHO)
- International Conference on Harmonization (ICH)
- Pan American Health Organization (PAHO)
- World Trade Organization (WTO)
- World Intellectual Property Organization (WIPO)

They also play significant role in applying pharmaceutical regulations in all aspects related to drug development, registration, production, distribution, marketing, price control and research. They also ensure and increase regulatory implementation in unregulated parts of the world for safety of public [5].

Drug Regulatory Agency in India:

Central Drugs Standard Control Organization (CDSCO):

CDSCO is the National Regulatory Authority (NRA) of India. It works under the Directorate General of Health Services (DGHS), Ministry of Health & Family Welfare; Government of India. The CDSCO is the central drug regulatory authority for execution of functions assigned to the central government under the Drugs and Cosmetics Act. CDSCO head office is located in New Delhi. CDSCO and state regulatory bodies are jointly responsible for grant of licenses of blood and blood products, intravenous fluids, vaccines and sera. Within the CDSCO, Drug Controller General of India (DCGI) is responsible for regulation of pharmaceutical products and medical devices. The Drug Technical Advisory Board (DTAB) and the Drug Consultative Committee (DCC) advise the DCGI. Licensing and classification of Medical devices is the function of the Central Licensing Approval Authority (CLAA). It is also responsible for setting and enforcing safety standards, performing post-market surveillance, issue of warnings and recall of pharmaceutical products for adverse events [5-7].

Functions of CDSCO: [6]

- **Central licensing authorities are responsible for:**
  - New drugs approval
  - Performing clinical trials
  - Establishing standards for drugs
  - Quality Control of imported drugs, import registration and licensing
  - Coordination of the activities of state drug control authorities by giving expert opinion to uniformly enforce the D&C Act
- **State licensing authorities are responsible for:**
  - Regulation of production, sale and marketing of drugs
- **Other Functions:**
  - Grant of license for blood banks, Large Volume Parenteral (LVP), vaccines, recombinant DNA products and some medical devices
  - Amendment of D & C Act rules
  - Ban of old drugs and cosmetics
  - Grant of test license, personal license, No Objection Certificate (NOC) for export
  - Testing of new drugs and cosmetics

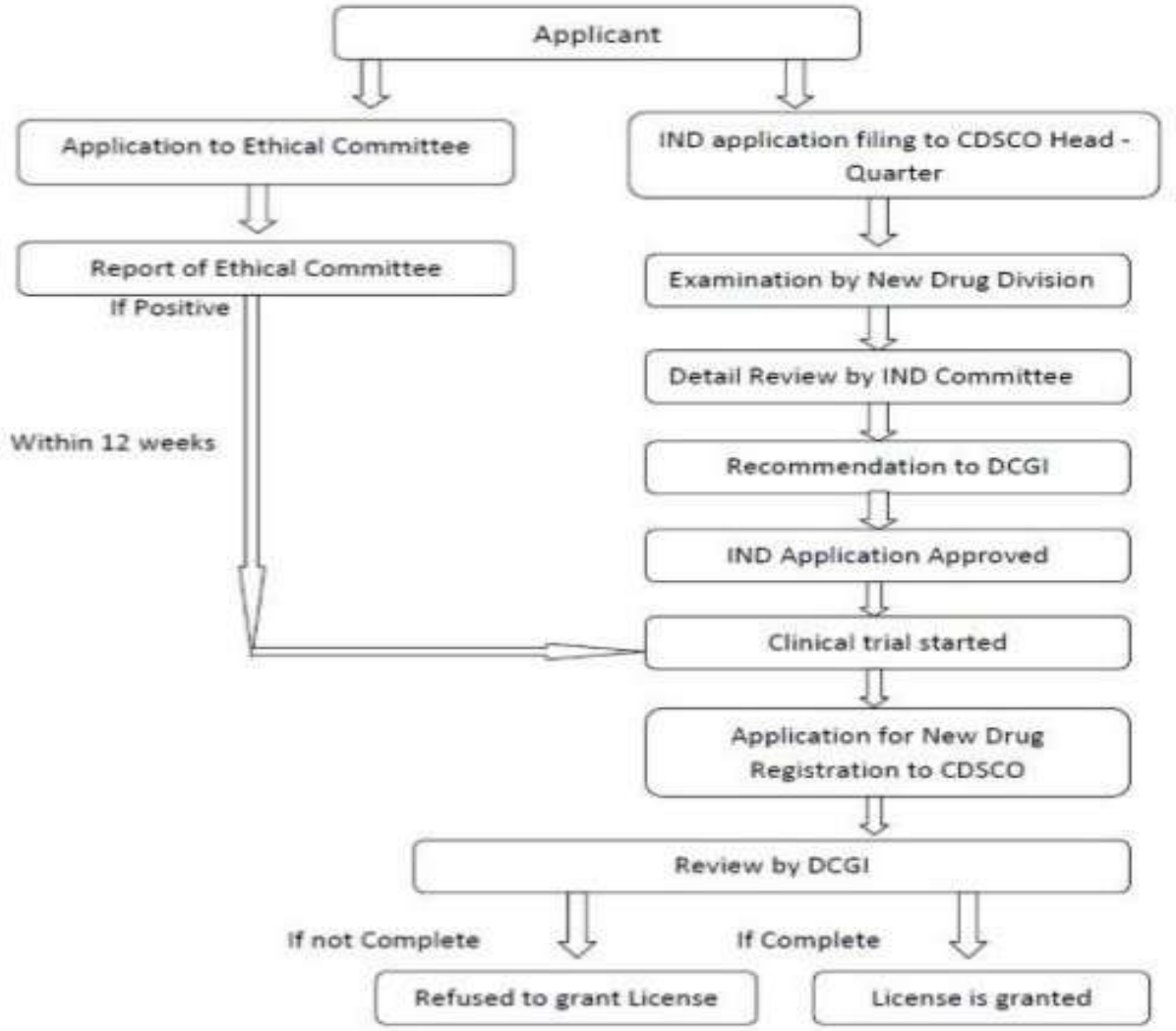
Functions of Central Drug Testing Laboratories: [6]

- Acts as an appellate authority in drug quality related disputes
- Procurement, preservation and distribution of international reference standard pharmaceutical substances

- Preparation of national reference standard pharmaceutical substances and microbial cultures useful in pharmaceutical analysis. And also distribution of standard drugs and cultures to state QC laboratories and pharmaceutical manufacturing establishments
- Training of analysts appointed by state drug control laboratories and other institutions
- Training of WHO personnel from abroad on advanced analytical methods
- Advises the central drug control authorities with respect to quality and toxicity of drug awaiting license
- To work out analytical specifications for monograph preparation for the Indian Pharmacopoeia and the Indian Homoeopathic Pharmacopoeia
- Additionally the CDL also associates with the WHO in preparing standards and specifications for International Pharmacopoeia
- Research and analysis of drug and cosmetics
- Registration samples analysis for site registration approval as per Good Manufacturing Practices (GMP)
- To take up analytical research on standardization of drugs

Drug approval process in India: For manufacture or import of a new drug, the company should obtain permission from the licensing authority (DCGI) by filing in Form 44 and submitting the necessary data according to Schedule Y of D&C Act 1940. Fig. 1 shows the drug approval process in India. To prove the efficacy and safety of imported drug in Indian population, clinical trials are conducted as per the Schedule Y guidelines and the report is submitted in specified format. DCGI reviews the application and approves if acceptable [7].

Fig. 1: Flow chart of drug approval process in India [7]



Schedule Y of D&C Act 1940 and Rules 1945:

- Section 2.4 (a) of Schedule Y says for those drug substances which are discovered in India all phases of clinical trials must be performed.
- Section 2.4 (b) of Schedule Y says that for those drug substances which are discovered in foreign countries; the applicant should submit the data available from those countries and the licensing authority may ask him to repeat all the studies or may permit him to proceed from Phase III.

- Section 2.8 of Schedule Y says that the licensing authority may require Pharmacokinetic studies (Bioequivalence studies) first to confirm that the data generated in Indian population is equal to data generated abroad and then require him to proceed with Phase III.

The exact requirements of clinical trials may vary from case to case and depending on the extent to which licensing authority is satisfied about its safety and efficacy. New drug approval in India is a very complicated process, which should meet necessary requirements along with New Drug Application to Food and Drug Administration (FDA) [6-7].
There is provision in Rule 122A of D&C Act 1940, that certain trails may be waived off if:

- the licensing authority considers that in the interest of public
- may grant permission for import of drugs based on the data of the clinical trials conducted in other countries
- in the case of drugs which are approved and being used for many years in other countries[8]

Drugs & Clinical Trials New Rules 2019:
The new rules reduce the time to one month for approving drugs manufactured in India and to 90 days for those developed in foreign countries. The rules also waive off the need for conducting a local Clinical Trial (CT) if the drug is approved for marketing in countries mentioned by the DCGI. The DCGI has waived off the CTs for the drugs approved in the European Union, United Kingdom, Australia, Canada, Japan and the United States. The new rules aim to encourage clinical research in India by providing transparent and effective regulations for CT and by assuring faster accessibility of new drugs to the Indian population [9].

Drug Regulatory agency in USA:

Food and Drug Administration:

The Food and Drug Administration (FDA) is an agency of United States Department of Health and Human Services. It consists of 6 product centers, 1 research center, and 2 offices. The Center for Drug Evaluation and Research (CDER) ensures that safe and effective drugs are available to enhance the health of the people. Food and Drug Modernization Act states that the FDA has 4 roles:

- To improve health by reviewing research and new products approval
- To assure that foods and drugs are safe and properly labelled
- To work with other countries to decrease the burden of regulation
- To cooperate with scientific experts and consumers to properly implement these obligations

The Commissioner of Food and Drugs, who is appointed by the President, leads the FDA. The FDA was empowered by the US Congress to enforce the Federal FD&C Act. The FDA has its headquarters in unincorporated White Oak, Maryland. The agency also has 223 field offices and 13 laboratories throughout the 50 states [10].

Functions of FDA: [10]

- Protecting and improving public health by control and supervision of:
    - Food (dietary supplements, food additives etc.,)
    - Drugs including both prescription and over the counter (non-prescription) drugs
    - Biological products like vaccines, blood & blood products
    - Cellular & gene therapy products
    - Allergenic, tissue and tissue products
    - Medical devices and Electromagnetic Radiation Emitting Devices (ERED)
    - Cosmetics, animal foods and veterinary medicines
    - Tobacco products
- Protecting the public health by ensuring that foods are safe and wholesome
- Helping to fasten product discovery or innovations

Drug approval process in United States:

Investigational New Drug (IND) Application: [11-13]

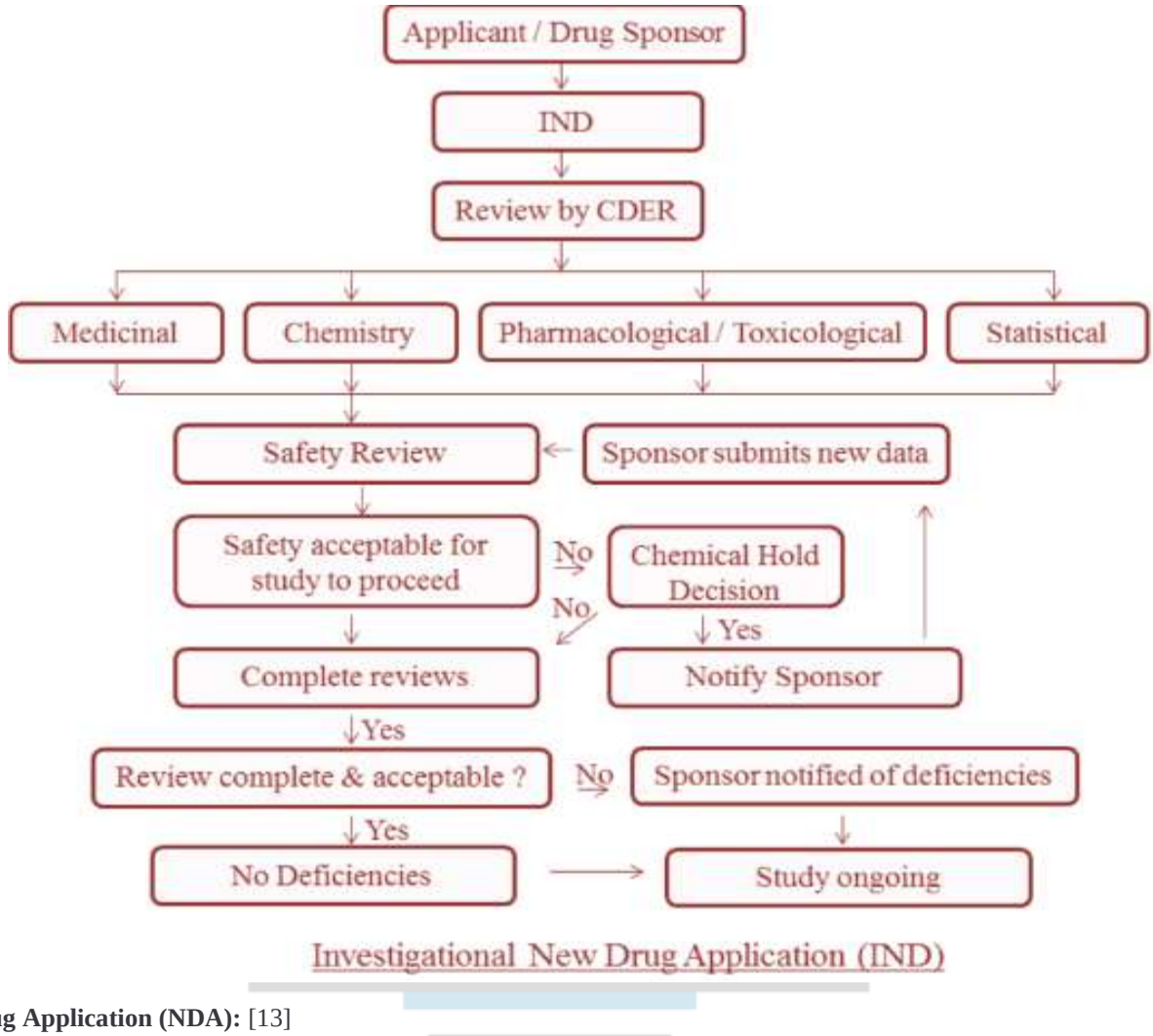
After drug discovery, preclinical trials are performed and results are reported. If the drug is found to be safe the drug developer (or) sponsor files IND application to the FDA in order to initiate clinical trials in humans volunteers. IND applications require information regarding animals used for pre-clinical studies, toxicological studies, and data including the composition, manufacturer, stability and clinical protocols of the trial. After approval of IND application, the investigators of the clinical trial can distribute a drug to multiple study locations across the US. IND application approval process is represented in fig. 2. A pre -IND meeting can be arranged with the FDA to discuss on issues like design of animal studies, intended study protocol for conducting the trials and chemistry, production & control of the IND. Such a meeting will help the drug developer or sponsor to organize animal research, gather information, and design the study protocol based on recommendations by the FDA. There are three types of IND applications: Investigator IND, Emergency Use IND (EIND), and treatment IND.

The investigator IND: A physician, sometimes on behalf of an institution/sponsor, files an investigator IND application. The investigator must wait minimum one month after submission of an IND application, in order to start any clinical trials. If the FDA does not have any objection, within that time Phase-I clinical trials can be started.

The EIND: An EIND application requests for FDA approval to utilize an experimental drug in an emergency when there is no sufficient time for following a standard IND process.

Treatment IND: Treatment IND applications are filed for approval to make use of an investigational new drug that shows promise in clinical trials prior to study completion, FDA review and final approval. These are also called Expanded use INDs.

Fig. 2: Flow chart of Investigational New Drug Application [13]



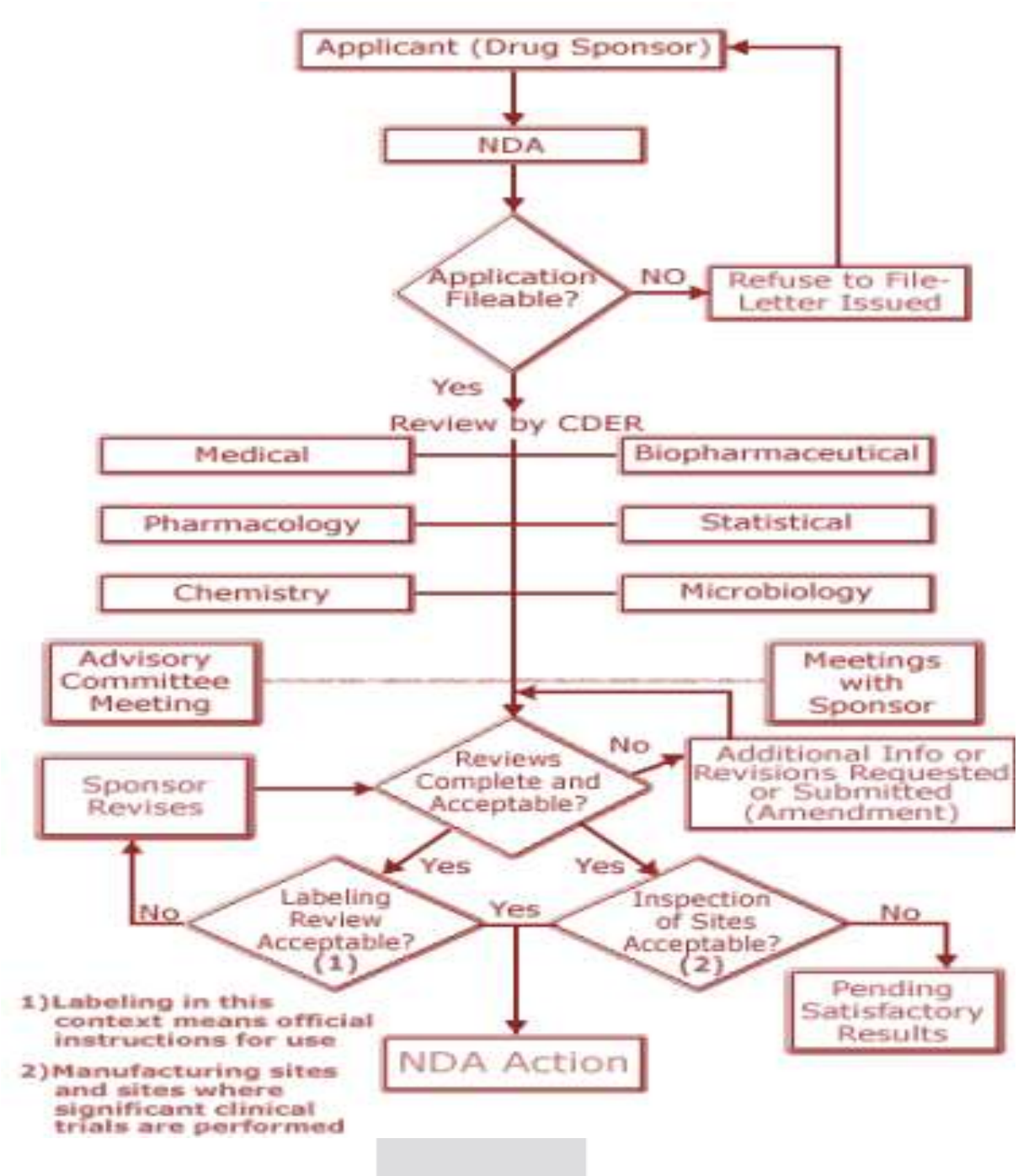
New Drug Application (NDA): [13]

The manufacturer files a NDA, if the clinical studies prove that a new drug is safe (without any unwanted or toxic effects) and effective. It is the actual request to produce and sell the drug in the US. NDA is submitted based on FD&C Act 505(b). NDAs are submitted for:

- New molecular entity (NME)
- New formulation of previously existing approved drug
- New combination of multiple drugs
- New indication (claim) for existing drug

The NDA application requires all data regarding the drug, manufacturing process, facilities, quality control & quality assurance, product description, packing and labeling. FDA personnel will assess clinical data, tests drug samples, audit the manufacturing facilities, and check labelling. FDA review completes within 180 days of receipt of application. Fig. 3 describes NDA application approval process. If FDA denies approval of the NDA, it sends a response letter including specific deficiencies and recommendations for the applicant in order to make the application viable. Unsuccessful applicants can request a hearing. Post approval of the NDA, the applicant can manufacture and market the drug.

Fig. 3: Flow Chart of New Drug Application [13]

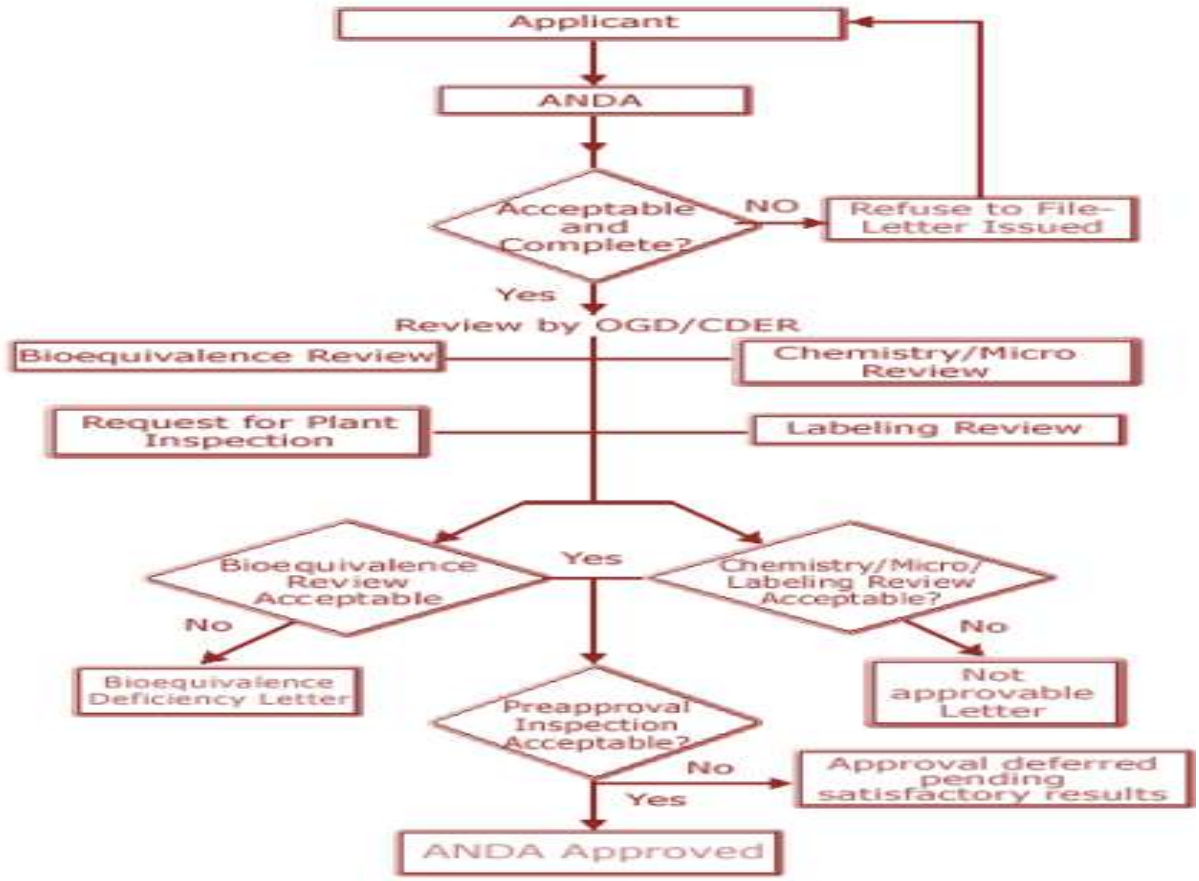


Abbreviated New Drug Application (ANDA): [13-14]

ANDA is an application filed for approval of generic drug product. The sponsor is not required to repeat the clinical studies that were done for the original/brand name drug product. Instead of this, generic drug product manufacturers must prove that their product is bioequivalent to, an already approved brand name product. Therefore, the generic drug applications are termed "abbreviated". Based on FD&C Act 505(j) ANDA is submitted.

ANDAs are submitted for generic drugs to which NDA must be approved previously and listed (known as the Reference Listed Drug). ANDA may not be submitted up to five years after the date of the approval of the NME. After approval, an applicant may produce and market the generic drug product to provide a safe, effective and lower cost alternative medicine to the public. All approved drug products (innovator and generic) are listed in Orange Book (FDAs Approved Drug Products with Therapeutic Equivalence Evaluations).

Fig. 4: Flow chart of Abbreviated New Drug Application



Drug Regulatory Agency in Europe:

European Medicines Agency (EMA): EMA is a European Union (EU) agency which evaluates and supervises medicinal products. Before 2004, it was known as the European Agency for the Evaluation of Medicinal Products or European Medicines Evaluation Agency (EMEA). The EMA was established in 1995 with funding from the EU and the pharmaceutical industry, as well as indirect subsidy from member states, in order to harmonize the work of existing national regulatory bodies for medicines. The EMA is a decentralized body located in London, before UK's withdrawal from the EU. It was relocated to Amsterdam in March 2019. The EU is presently the source of about 1/3rd of the new drugs brought onto the international market each year [15].

Functions of EMA:[16]

- Provides timely patient access to new medicines
- Scientific suggestions and protocol assistance
- Orphan designation of medicines for rare diseases
- Developing scientific guidelines on needs for the safety, efficacy and quality testing of medicines and setting standards
- Promotes research and development of new medicines in the pharmaceutical industry by European small and medium sized enterprises
- Continuous monitoring and supervision of the safety of medicines
- Assessment of pharmaceutical manufacturing companies' compliance with their Pharmacovigilance (PV) obligations
- Contributes to international PV activities with other authorities outside the EU
- Provides information on the safety of medicines to the public
- Publishes impartial and clear information about medicines and their approved uses

What EMA does not do? [16]

- Evaluation of the initial MAA of all medicines in the EU
- Evaluation of applications for the authorization of clinical studies
- Evaluation of medical devices
- Evaluation of food supplements and cosmetics
- Carry out research or development of medicines
- Take decisions on the price or medicines availability
- Control the advertisement of medicines

Pathways for drug approval in EU: [17-20]

Similar to the US FDA requirements, there are two regulatory steps to go through prior to approval of a drug for marketing in the EU. These two steps are clinical trial application and marketing authorization application. In the EU there are 28 member states; clinical trial applications approval is done at the member state level, whereas MAA are approved at both the member state and centralized levels. Approval for manufacture and marketing of a drug can be obtained by any of the following four procedures, depending on the drug class and the preference of the manufacturer:

- Centralized process
- National process
- Mutual recognition
- Decentralized procedure

Centralized process: This process allows applicants to obtain a marketing approval that is valid in all the EU member states. EMA opinion issued within 210 days after filing application, and submitted to European Commission for final approval. Centralized process is mandatory for the medicines that are:

- derived from biotechnology processes (genetic engineering)
- used for the treatment of cancer, HIV/AIDS, diabetes, neuro-degenerative disorders/autoimmune diseases and immune system dysfunctions
- officially designated 'Orphan medicines' which are used for rare diseases

This process is controlled through the EMA. Every EU member state is represented on the EMA Committee for Medicinal Products, which provides a single license valid in all EU member states.

National process: This procedure allows applicants to attain a marketing authorization in only one member state. To obtain a marketing authorization in a country, 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 approval under this procedure. Timeline for issue of EMA opinion is 210 Days. Each EU state can have its own procedures for approving drugs that fall outside of those needed to undergo the centralized process.

Mutual recognition: This process permits applicants to get a marketing authorization in the Concerned Member States (CMS) other than the Reference member state (RMS), where the drug is already approved. Applicant must submit identical dossier to all the EU member states in which they want to obtain marketing approval, along with required information.

As soon as one of the member states decides to evaluate the medicinal product (at which point it will become the RMS), it will inform this decision to other member states (which then will become the CMS), to which applications have also been submitted. RMS issues a report to other states on its own findings after completion of evaluation. Generic drug industry is the major user of this type of drug approval process. Time line for issuing the EMA opinion is 390 days.

Decentralized procedure: Using this procedure, pharmaceutical industry may apply for marketing authorization at a time in more than one EU country for medicinal products that have not yet obtained authorization in any EU country and essentially do not fall within the centralized procedure's essential list of drugs. In this decentralized procedure, according to the decision taken by the RMS & CMS the marketing authorization should be granted. Generally used for those medicinal products that did not receive any authorization in an EU country. Time taken for issue of EMA opinion is 210 days.

Advantages of decentralized: The applicant is not needed to go through the entire process of dossier filing, queries, reply to queries and approval repeatedly in order to obtain approval in multiple member countries of the EU. Approval in multiple countries through single procedure. Time taken for approval in multiple EU member countries can be minimized and costs can be reduced.

Table 2: Comparison between US, EU and India regulatory submissions [21]

Requirements	**India**	**US**	**Europe**
Agency	One agency DCGI	One agency USFDA	Multiple Agencies: EMEA, CHMP and National Health Agencies
Registration Process	One registration process	One registration process	Multiple Registration Process: 1. Centralized 2. Decentralized 3. Mutual recognition 4. National
Application	MAA	ANDA/NDA	MAA
Debarment Classification	Not required	Required	Not required
No. of copies	1	3	1
Approval timeline	12 to 18 months	18 months	12 months
Fees	50000INR	Under $ 2 million for NDA Application and $ 51,520 for ANDA Application	National fee (including hybrid application): € 103,059; Decentralized procedure where UK is CMS: €99507

Common Technical Document (CTD):

A single regulatory approach for filing MAA of new drug product applicable to various countries (based on single dossier) is very difficult as different countries have different regulatory approaches for approval of a new drug. Therefore, the details of regulatory requirements of each country should be known for filing application for marketing approval. CTD was developed with an objective to provide a format, which is common for the technical documentation to file applications for registration of pharmaceuticals. Initiations by European regulatory body in conjunction with USA and Japan have approached the common document called CTD dossier for the documentary submission [22-25].

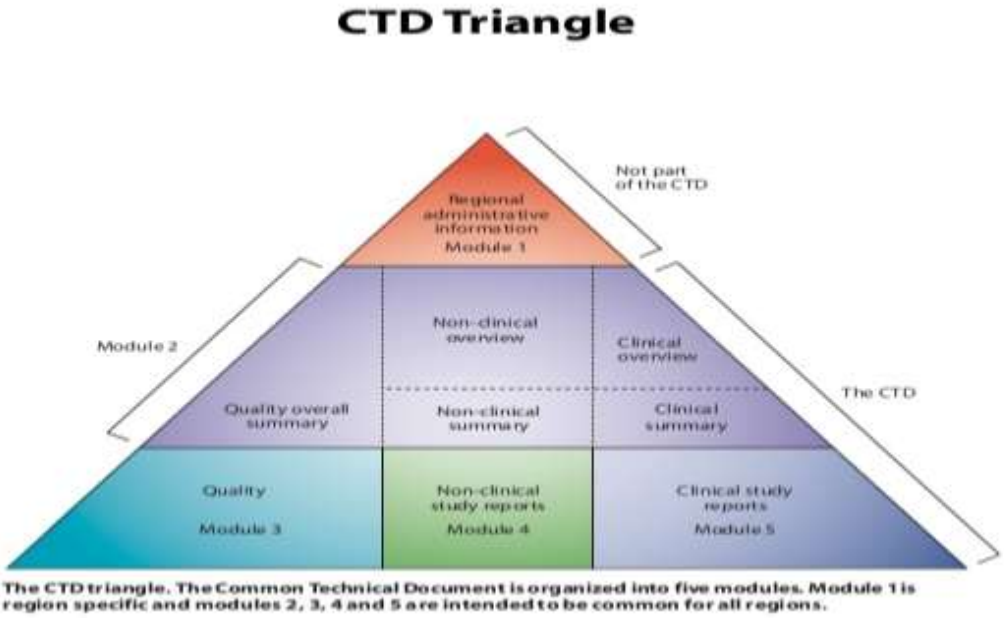
CTD format is agreed globally for the preparation of applications related to new drugs intended to be submitted to regulatory bodies in participating countries. It is a set of specifications for application dossier for the registration of medicinal products and is used across Europe, Japan and US. ICH M4 Expert Working Group has developed it. The agreement to compile all the efficacy, safety and quality data in a common format (called CTD) has revolutionized the regulatory review process, led to harmonized electronic submission (eCTD) which, in turn, allowed implementation of good review practices. ECTD is the electronic version of CTD, which was adopted by US, EU, Japan and Canada [25].

CTD - Modules: [25]

The CTD dossier is categorized into five main modules:

- Module 1 - Administrative and prescribing information
- Module 2 - Summaries of Modules 3–5
- Module 3 - Quality (pharmaceutical documentation)
- Module 4 - Non-clinical study reports (pharmacology/toxicology)
- Module 5 - Clinical trial reports

Fig.5: Common Technical Document Triangle



Benefits: [22-25]

- Significant reduction in time and resources needed to compile applications for complete submissions
- For pharmaceutical industries, it eliminates the need to reformat the information for submission to the different regulatory agencies
- Would simplify the preparation of electronic submissions
- Easier analysis across applications
- Paper storage can be reduced by archiving in electronic form
- Faster access and easy retrieval of information
- Improved staff productivity
- High security for the data through restricted access
- Saves time and money by reducing the need to print the documents

CONCLUSION: The drug approvals in the US, Europe and India are the most demanding in the world. The primary purpose of the rules governing pharmaceutical products is to safeguard public health. It is the role of regulatory authorities to ensure that pharmaceutical companies comply with regulations so that the drugs developed and manufactured will be safe, effective and thus the patient's well-being is protected.

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