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ROLE AND OVERVIEW OF DRUG REGULATORY AFFAIRS IN PHARMACEUTICAL INDUSTRY WITH IMPLEMENTATION OF CTD AND ECTD

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ABSTRACT

Drug Regulatory affairs is a vital unit in a pharmaceutical Industry. As the Pharmaceutical sector is rising very rapidly, there is a need of regulatory affairs professionals to provide the current needs of industries for the global competition. Drug Regulatory affairs professionals are the crucial link between pharmaceutical industries and worldwide regulatory agencies. Pharmaceutical product approval process should be a critical step in ensuring access to safe and effective drugs. Central Drugs Standard Control Organization (CDSCO), India has decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use. Implementation of CTD is expected to significantly reduce time and resources needed by industry to compile applications for global registration. This present article discusses the evolution of Drug Regulatory Affairs, its role in Pharmaceutical industry and its involvement for the implementation of CTD guidelines to regulate the marketing of the drugs and improve the growth of the industry.

KEYWORDS: Regulatory Affairs, Regulatory Agencies, ICH guidelines, Drug Approval Process, CTD, eCTD.

INTRODUCTION

A regulatory affair (RA) is a profession which acts as the interface between pharmaceutical industry and drug regulatory authorities across the world. It is mainly involved in the registration of drug products in respective countries prior to their marketing. The drug regulatory af-

fairs department is an important part of the organisational structure of pharmaceutical companies.

The Pharmaceutical Industry is well organized, systematic to international regulatory standards for manufacturing of Chemical and Biological drugs for human and veterinary consumption as well as medical devices, traditional herbal products and cosmetics.[1]

The drug regulatory affairs professional plays an important role in every phase from developing regulatory strategies following the discovery of a new chemical entity to planning post-marketing activities.[12]

A new molecule can cost several millions of rupees or dollars to progress in pharmaceutical industries and any blunder causes greater impact on company's status. As medicines play a vital role in human's life there must be regulations for medicines ensuring Quality, Safety and Efficacy of drugs. The regulatory affairs professional is completely responsible for holding products in compliance and maintaining all the records and documents. Even a small mistake in any of the activities related to regulatory, quality and safety can make the product to be recall in addition to loss of several millions of the money.

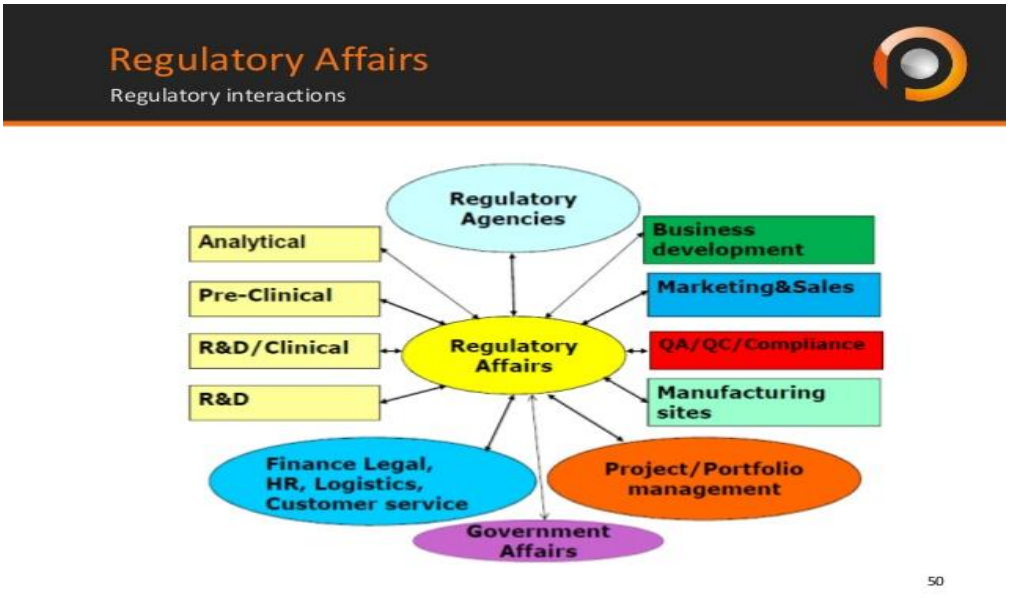

Fig. 1. Overview of Regulatory Affairs.

Drug development in all aspects to commercialization is highly regulated. Every drug before getting market approval must undergo clinical trials to ensure its safety, efficacy and quality. Some of these standards are set by regulatory authorities of their respective countries.

Regulation overall affects all aspects of the pharmaceutical world, from independent innovators and pharmaceutical companies to regulatory and administrative bodies and patients also. Regulatory department is link between company, products and regulatory authorities whose positive or negative point foster the insight of the regulatory authority into the industry, for good or for bad. So, the better the scientific precision, the greater will be the chances for a product to come to the market within the expected time.[2]

OBJECTIVES OF REGULATORY AFFAIRS

- How and why the pharmaceutical industry and drug regulations have developed in USA.
- The Rules Governing Medicinal Products in the European Union.
- Major Regulations of USA.
- Framework of EU and its regulatory.
- Pharmaceutical Legislations of EU.
- Indian Pharmaceutical Industry & Drug Regulations development in different Era.
- Types of Marketing Authorization Procedure in EU Market.
- Major Rules and Act of India.
- Roles of Regulatory Affairs Professional in Health Authorities as well as Pharmaceutical Industry.
- Ensuring that their companies comply with all the regulations and laws pertaining to their business.
- Working with federal, state and local regulatory agencies and personnel on specific issues affecting their business.
- Advising companies on the regulatory aspects and climate that would affect their proposed activities.[3]

REGULATORY AFFAIRS IN PHARMACEUTICAL INDUSTRY

The regulatory affairs personnel work hand in hand with marketing and R&D to develop, innovative products that take advantage of new technological and regulatory developments to accelerate time to market. With new products expected to add significant revenues to the company's bottom lines, small decreases in time to market equate to large material gains in revenue and profit. Employing adaptive clinical trial strategies, obtaining quick approval from regulatory authorities and avoiding pitfalls in processes can accelerate development of new products and help to reduce costly errors and time lags.[4]

REGULATORY BODIES IN THE WORLD[2]

Table 1: Different regulatory bodies in the world.

Country	Regulatory Authority
India	Central Drugs Standard Control Organization Drug controller general of India (DCGI)
US	Food and Drug Administration (US FDA)
UK	Medicines and Health care products regulatory Agency (MHRA)
Australia	Therapeutic Goods Administration (TGA)
Japan	Japanese Ministry of Health, Labour and Welfare (MHLW)
Canada	Health Canada
Brazil	Agency Nacional degradation Vigilancia Sanitaria (ANVISA)
South Africa	Medicines Control Council (MCC)
Europe	European Directorate for Quality of Medicines (EDQM)
	European Medicines Evaluation agencies (EMEA)

Regulatory Affairs professionals give strategic and technical advice to R&D, Production, QC department etc. right from the beginning of the development of a product, making an important contribution both commercially and scientifically to the success of a development programme and company. It takes up to 15 years to develop and launch a new pharmaceutical product and many problems may arise in the process of scientific development and because of a changing regulatory environment. Regulatory professionals help the company to avoid problems caused by irrelevant records, inappropriate scientific thinking or poor presentation of data.[1]

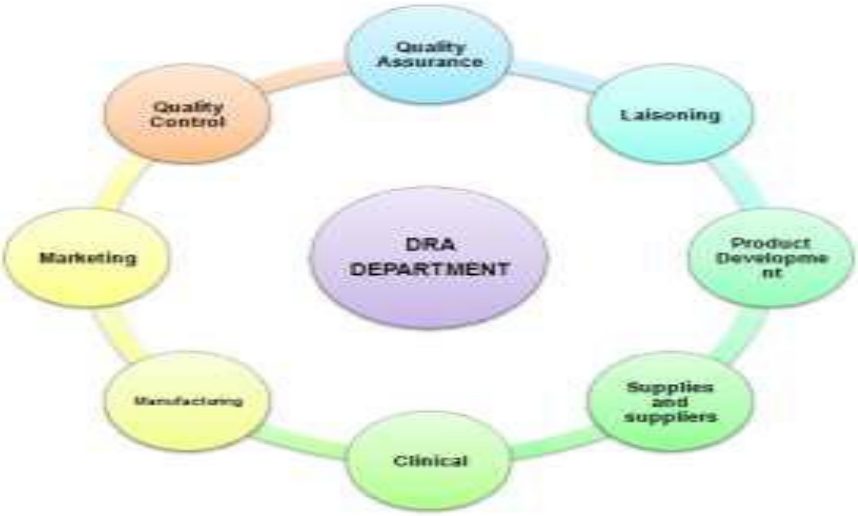

Fig. 2. Involvement of Regulatory Affairs in Pharmaceutical Industry.

INTERNATIONAL CONFERENCE ON HARMONISATION (ICH)

ICH stands for the "International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use". ICH is a joint initiative involving both regulators and research-based industry representatives of the EU, Japan and the US required to assess and ensure the safety, quality and efficacy of medicines.[5] The objective of ICH is to increase international harmonization of technical requirements to ensure that safe, effective, and high quality medicines are developed and registered in the most efficient and cost effective manner.

Members of ICH

ICH mostly comprises of Six Parties that are directly involved, as well as three Observers and IFPMA. The Six Parties are the founder members of ICH which represent the regulatory bodies and the research-based industry in the European Union, Japan and the USA. These parties include the EU, MHLW, FDA, EFPIA, PhRMA and JPMA.

The Observers are WHO, EFTA (Currently represented at ICH by Swissmedic Switzerland), and Canada (represented by Health Canada). This important group of non-voting members acts as a link between the ICH and non-ICH countries and regions.[13]

ICH GUIDELINES

ICH has developed over 45 harmonized guidelines. The ICH guidelines are divided into four major categories:

1. Quality (Q): Those relating to chemical and pharmaceutical Quality Assurance.

2. Safety (S): Those relating to in vitro and in vivo preclinical studies.
3. Efficacy (E): Those relating to clinical studies in human subject.
4. Multidisciplinary (M): Cross-cutting Topics which do not fit uniquely into one of the above categories.[14]

COMMON TECHNICAL DOCUMENT (CTD)

The Common Technical Document (CTD) is a set of specification for application dossier for the registration of Medicines and prepared to be used across Europe, Japan and the United States. It is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional authorities in the countries. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, U.S.) and the Ministry of Health, Labour and Welfare (Japan). The CTD is maintained by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).[6]

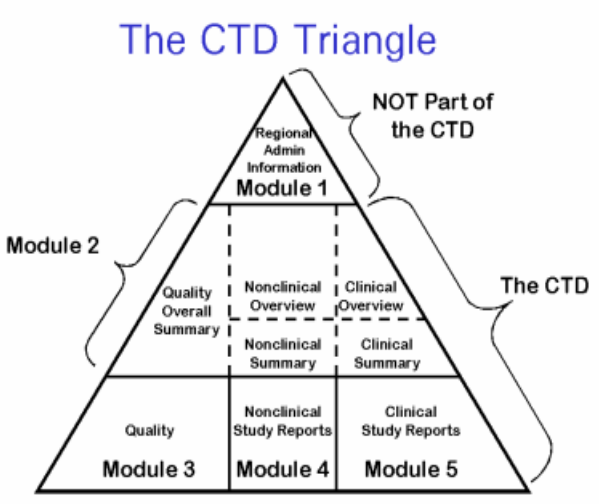

Fig. 3: CTD Triangle.

General Considerations for Dossier Preparation[7]

Table 2: Modular Organization of CTD.

The Common Technical Document	
Module 1: Administrative Information and Prescribing Information	
1.1	Table of Contents of the Submission Including Module 1
1.2	Documents Specific to Each Region
Module 2: Common Technical Document Summaries	
2.1	CTD Table of Contents
2.2	CTD Introduction
2.3	Quality Overall Summary

2.4	Nonclinical Overview
2.5	Clinical Overview
2.6	Nonclinical Written and Tabulated Summary □ Pharmacology □ Pharmacokinetics □ Toxicology
2.7	Clinical Summary □ Biopharmaceutics and Associated Analytical Methods □ Clinical Pharmacology Studies □ Clinical Efficacy □ Clinical Safety □ Synopses of Individual Studies
Module 3: Quality	
3.1	Module 3 Table of Contents
3.2	Body of Data
3.3	Literature References
Module 4: Nonclinical Study Reports	
4.1	Module 4 Table of Contents
4.2	Study Reports
4.3	Literature References
Module 5: Clinical Study Reports	
5.1	Module 5 Table of Contents
5.2	Tabular Listing of All Clinical Studies
5.3	Clinical Study Reports
5.4	Literature References

The CTD is mainly organized into 5 modules:

Module 1 is region specific & Modules 2, 3, 4, and 5 are intended to be common for all regions.

Module 1: Administrative Information

Administrative Information should contain documents specific to each region; e.g. application forms or the proposed label for use in the region.

Module 2: Quality Overall Summary

CTD Summaries Begin with a general introduction to the pharmaceutical (its pharmacological class, mode of action, proposed clinical use.

Module 3: Quality

The Quality section of the Common Technical Document (M4Q) provides a harmonised structure and format for presenting CMC (Chemistry, Manufacturing and Controls) information in a registration dossier. The table of contents includes sections on Drug Substance

and Drug Product as shown in Table 3 & 4. There are sections for regional specific informations as well as some appendices.

Table 3. Contents of Module 3 for Drug Substance[5]

SR.NO.	CONTENTS
3.2. S	**DRUG SUBSTANCE**
3.2.S. 1	**GENERAL INFORMATION**
	3.2.S. 1.1 Nomenclature
	3.2.S. 1.2 Structure
	3.2.S. 1.3 General Properties
3.2.S. 2	**MANUFACTURE OF DRUG SUBSTANCE**
	3.2.S. 2.1 Manufacturer(s)
	3.2.S. 2.2 Description of Manufacturing process and process controls
	3.2.S. 2.3 Controls of Material
	3.2.S. 2.4 Control of critical steps and Intermediates
	3.2.S. 2.5 Process Validation and/or Evaluation
	3.2.S. 2.6 Manufacturing Process Development
3.2.S. 3	**CHARACTERIZATION OF DRUG SUBSTANCE**
	3.2.S.3.1 Elucidation of structures and other characteristics
	3.2.S.3.2 Impurities
3.2.S.4	**QUALITY CONTROL OF DRUG SUBSTANCE**
	3.2.S.4.1 Specification and Justification of specification
	3.2.S.4.2 Analytical Procedures
	3.2.S.4.3 Validation of Analytical Procedures
	3.2.S.4.4 Batch Analyses
3.2.S.5	**REFERENCE STANDARDS OR MATERIALS**
3.2.S.6	**CONTAINER CLOSURE SYSTEM**
3.2.S.7	**STABILITY OF DRUG SUBSTANCE**
	3.2.S.7.1 Stability summary and conclusions
	3.2.S.7.2 Post-approval stability protocols and Commitments
	3.2.S.7.3 Stability data

Table 4. Contents of Module 3 for Drug Product

SR.NO	CONTENTS
3.2. P	**DRUG PRODUCT**
3.2.P.1	**DESCRIPTION AND COMPOSITION**
3.2.P.2	**PHARMACEUTICAL DEVELOPMENT**
	3.2.P.2.1 Components of drug product
	3.2.P.2.1.1 Drug Substance
	3.2.P.2.1.2 Excipients
	3.2.P.2.2 Drug Product
	3.2.P.2.2.1 Formulation & development
	3.2.P.2.2.2 Overages
	3.2.P.2.2.3 Physicochemical & Biological properties
	3.2.P.2.3 Manufacturing process Development
	3.2.P.2.4 Container-Closure System
	3.2.P.2.5 Microbiological Attributes

	3.2.P.2.6 Compatibility
3.2.P.3	**MANUFACTURE OF DRUG PRODUCT**
	3.2.P.3.1 Manufacturer(s)
	3.2.P.3.2 Batch Formula
	3.2.P.3.3 Description of Manufacturing process and process controls
	3.2.P.3.4 Control of critical steps & Intermediates
	3.2.P.3.5 Process Validation and/or Evaluation
3.2.P.4	**CONTROL OF EXCIPIENTS**
	3.2.P.4.1 Specifications and Justification of Specifications
	3.2.P.4.2 Analytical Procedures
	3.2.P.4.3 Validation of Analytical procedures
	3.2.P.4.4 Excipients of human or animal origin
	3.2.P.4.5 Excipients used for the first time
3.2.P.5	**CONTROL OF DRUG PRODUCT**
	3.2.P.5.1 Specifications and Justification of Specifications
	3.2.P.5.2 Analytical Procedures
	3.2.P.5.3 Validation of Analytical procedures
	3.2.P.5.4 Batch Analyses
	3.2.P.5.5 Characterisation of Impurities
3.2.P.6	**REFERENCE STANDARDS OR MATERIALS**
3.2.P.7	**CONTAINER CLOSURE SYSTEM**
3.2.P.8	**STABILITY OF DRUG SUBSTANCE**
	3.2.P.8.1 Stability summary & conclusions
	3.2.P.8.2 Post-approval stability protocol and Commitment
	3.2.P.8.3 Stability data

Module 4: Non-clinical / preclinical study reports

The CTD Safety (M4S) Guideline delineates the structure and format of the nonclinical summaries in Module 2 of the Common Technical Document, and provides the organisation of Module 4, the Nonclinical Study Reports. The Nonclinical Overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic, and toxicologic evaluation of the pharmaceutical, and generally should not exceed 30 pages. The Nonclinical Written Summaries (100 – 150 pages) are recommended to provide more extensive summaries and discussion of the nonclinical information on pharmacology, pharmacokinetics and toxicology.

Module 5: Clinical Study Reports

CTD-Efficacy (M4E) describes the structure and format of the clinical data in an application, including summaries and detailed study reports. There are two high level clinical summaries in Module 2 of the CTD: The Clinical Overview, a short document that provides a critical assessment of the clinical data; and the Clinical Summary, a longer document that focuses on data summarization and integration. Clinical Study Reports as well as raw data are included in Module 5.

ADVANTAGES OF CTD[7]

1. The main aim behind implementing a common format of submission is to make the reviewing of each application easier and to avoid omission of critical data or analyses. Omissions of such data can result in unnecessary delays in approvals.
2. A common format for the technical documentation will significantly reduce time and resources needed to compile applications for registration of human pharmaceuticals and will ease the preparation of electronic submission.
3. Regulatory reviews and communication with the applicant will be facilitated by a standard document of common elements.
4. Implementation of CTD is expected to significantly reduce time and resources needed by industry to compile application for global registration.
5. CTD not only help in raising the Indian standard but also will help to bring a proper structure to the whole process of filling an application.
6. In addition, exchange of regulatory information between regulatory authorities will also be simplified.

SILENT BENEFITS OF CTD

1. Global harmonization of applications.
2. Provides standards to prepare submission-ready documents in the IND phases.
3. Standardization assists project management and information management.
4. Facilitates life cycle management.
5. Facilitates drug development planning.

ELECTRONIC COMMON TECHNICAL DOCUMENT (eCTD)

The electronic Common Technical Document (eCTD) is an interface for the pharmaceutical industry to agency transfer of regulatory informations. Main Content is based on the Common Technical Document (CTD) format. It was developed by the International Conference on Harmonisation (ICH) Multidisciplinary Group 2 Expert Working Group (ICH M2 EWG).[8] Essentially, the electronic Common Technical Document (eCTD) will be a transport format intended to be moved into an agency's review environment and will facilitate electronic submissions. The eCTD will serve as an interface for industry-to-agency transfer of regulatory information, and at the same time take into consideration the facilitation of the creation, review, life-cycle management and archiving of the electronic submission. The eCTD specifications list the criteria which will make an electronic submission technically

valid. The eCTD represents a major advance in the submission of information to support a new drug application. In the future, companies might be able to send their submissions to several regulatory authorities simultaneously with the single stroke of a computer key.[7]

BENEFITS OF eCTD[8]

1. Improved handling and archiving of submissions Benefits of eCTD
2. Better information management
3. Support of Life Cycle Management
4. Immediate Access to complete and up-to-date information
5. Search functionality for assessors and increased tracking ability
6. Facilitated evaluation and better visibility of the process
7. Reduced workload and reuse of information for assessment reports
8. Controlled communication with external experts
9. Better use of resources
10. Simplified business process
11. Better communication with industry

DRUG APPROVAL PROCESS

When a company wants to manufacture/ import a new drug it must apply to seek permission from the licensing authority (DCGI) by filing in Form 44 and submit the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. To prove its efficacy and safety in Indian population it must conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format. The process of approval of new drug in any country is a very complicated process. Further should meet necessary requirements along with NDA to FDA. The need of the present work is to study and document & maintain the requirements for the process of approval of new drug in India with emphasis on clinical trials as per Drugs Control department, Government of India.[9]

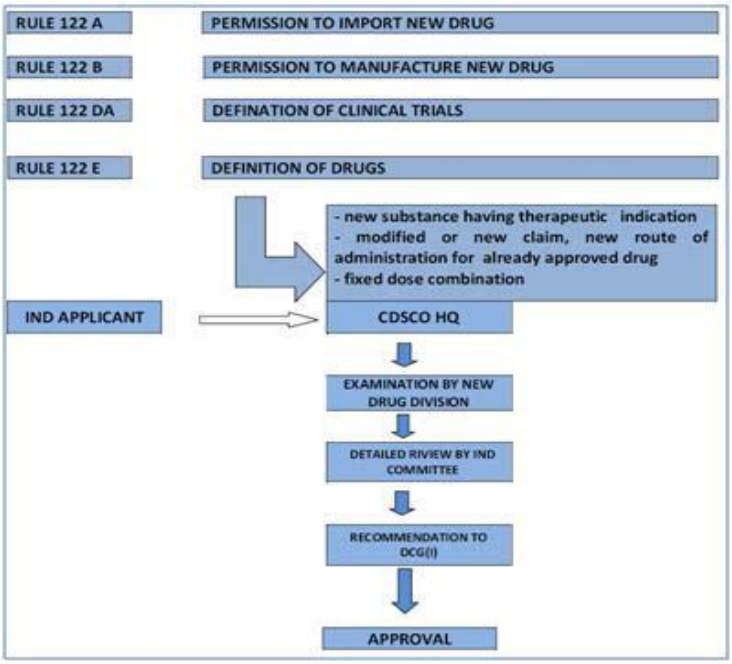

Fig 4: Pictorial representation drug approval process in India.

NEW DRUG APPLICATION

NDA is an application which is to be submitted prior to the FDA for permission to market a new drug. Further to obtain this permission a sponsor submits preclinical and clinical test data to NDA for analysing the drug information, description of manufacturing procedures.

After NDA received by the agency, it undergoes a technical screening and evaluation. This evaluation and documentations ensures that sufficient data and informations have been submitted in each area to justify "filing" the application that is FDA formal review. After FDA review of an NDA, there are 3 possible actions that can send to sponsor:

1. Not approvable- in this letter list of deficiencies and explain the reason.
2. Approvable - it means that the drug can be approved but minor deficiencies that can be corrected like-labelling changes and possible request commitment to do post-approval studies.
3. Approval- it states that the drug is approved.[9]

Different Phases of clinical trials[9]

- **Pre-clinical study** - Mice, Rat, Rabbit, Monkeys.
- **PHASE I** - Human pharmacology trial: Estimation of safety & tolerability.
- **PHASE II** - Exploratory trial: Estimation and evaluation of effectiveness and short term side effects.

- **PHASE III -** Confirmatory trial: Confirmation trials taken of therapeutic benefits.
- **PHASE IV –** Post-marketing trial: Studies which are done after drug approval.

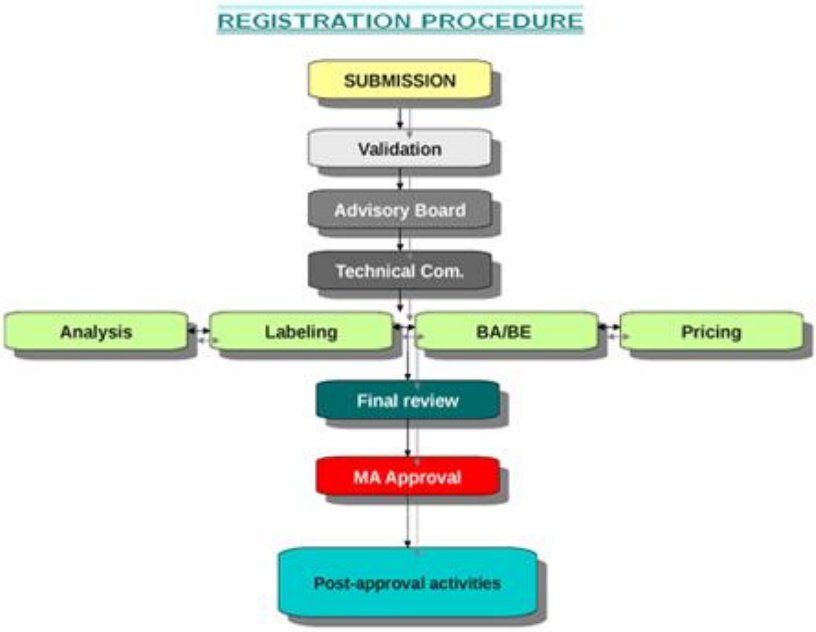

Fig. 5: NDA Registration Procedure.

Some of the rules & guidelines that should be followed for regulation of drugs in India are:

- Drugs and Cosmetics Act 1940 and its rules 1945
- Narcotic Drugs and Psychotropic Substances -1985
- Drugs Price Control Order 1995
- Consumer Protection Act-1986
- Factories Act-1948
- Law of Contracts (Indian contract Act-1872)
- Monopolistic & Restrictive Trade Practices Act-1969
- ICH GCP Guidelines
- Schedule Y Guidelines
- ICMR Guidelines
- Registry of Trial

CONCLUSION

Drug Regulatory Affairs department is constantly evolving and growing and is least impacted during the acquisition and merger, and during recession. Regulatory Affairs departments are growing within companies. Regulatory Affairs 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.

The proper implementation of regulatory guidelines and laws will improve the economic growth of the pharmaceutical industry and also improves the safety of the people.

In India, CDSCO adopted CTD format for technical requirements for registration of pharmaceutical products in 2009-2010. Still inspite of the CDSCO approval, there are certain companies that do not have knowledge about the primary requirements for preparation of dossier according to the CTD format. Since CDSCO guidelines made the filing of a dossier in CTD format compulsory in India, the above study emphasizes on how to prepare a dossier according to the CTD. CTD and eCTD significantly reduces the time and resources needed to compile applications for registration of human pharmaceuticals. Eases the preparation of electronic submissions.

From the above review, it can be concluded that the related information regarding the approval of new drug in India should provide the necessary requirements along with the NDA to FDA. The clinical studies report and related information for process of approval of new drug in India with emphasis on clinical trials should follow the Schedule Y, the Drug and Cosmetics Rules 1945 rules given by the CDSCO. Pharmaceutical product approval process should be a critical step in ensuring access to safe and effective drugs.[10]

In today's competitive environment the reduction of the time taken to reach the market is critical to a product's and hence within the companies for their success and growth.[11] Hence, the purpose. of this work is to gather knowledge about various technical document requirements and study of various guidelines supporting the drug approval process.

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REFERENCES

1. P. Praneeth. Regulatory Affairs and its role in Pharmaceutical Industry. International Journal of Pharmacy and Biomedical Engineering (SSRG-IJPBE). Jan-Feb, 2016; 3(1): 1-2.

2. Dolita Shah*, Mayur Mistry. Pharma tutor. https://www.pharmatutor.org/articles/an-overview-of-regulatory-affairs-and-its-importance-in-pharmaceuticals-other-industries.
3. Shivam Lale, Amol Kendre, Mayur Gandhi and Shreyas Dani. Role of drug regulatory affairs in Pharma Industry. World Journal of Pharmaceutical Research SJIF., 2015: 4(6): 615-625.
4. Subash Philip, Ansa Philip. The scope of Regulatory Affairs in the Pharmaceutical Industry. Hygeia Journal for Drugs and Medicines. April-Sep, 2010; 2(1): 1-6.
5. Naishi Kirtikumar*, Dr. Dilip Maheshwari. Documentation requirements for generic drug application to be marketed in India- a Review. Journal of Pharmaceutical Science and Bioscientific Research (JPSBR)., 2014; 4(4): 237-242.
6. From Wikipedia. http://en.wikipedia.org/wiki/common_technical_document.
7. Bhalodiya H. A.*, Boda J. M., Shah J. S., Patel P. B., Vaghela J. P. The Common Technical Document (CTD): Taking Indian NDA process towards Globalization. International Journal of Pharmaceutical Sciences Review and Research (IJPSRR). July–Aug: 2011; 9(2): 181-187.
8. Wikipedia. http://en.wikipedia.org/wiki/electronic_common_technical_document.
9. N. Vishal Gupta*, C. Mohan Reddy, K. Pradeep Reddy, R. Ajay Kulkarni, H.G. Shiva-kumar. Process of approval of new drug in India with emphasis on clinical trials. International Journal of Pharmaceutical Sciences Review and Research (IJPSRR). Mar–April: 2012; 13(2): 17-23.
10. Suresh S*, S.B Puranik, Phatru Patel. Regulatory Requirements for Registration of Pharmaceutical to Gain Market Access in India. RRJPPS. Oct–Dec: 2014; 3(4): 49-54.
11. Sumit kumar*, Rishabh Panwar, Upendra Singh. Regulatory Affairs in the Pharmacy Curriculum. International Journal of Research and Development in Pharmacy and Life Sciences. Oct– Nov: 2013; 2(6): 690-698.
12. Madeleine Pesant. Science- A Cosmological Conundrum. The Drug Regulatory Affairs Professional. Feb: 2018; 359(6375).
13. ICH.com http://www.ich.org/about/members-observers.html.
14. ICH.com http://www.ich.org/products/guidelines.html.