

**ROLE OF DRUG REGULATORY AFFAIRS IN PHARMA INDUSTRY****Shivam Lale<sup>1\*</sup>, Amol Kendre<sup>1</sup>, Mayur Gandhi<sup>2</sup> and Shreyas Dani<sup>3</sup>**

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**ABSTRACT**

Drug Regulatory Affairs (DRA) is a vital unit in a pharmaceutical company. It is concern about the healthcare product lifecycle, it provide strategic, tactical and operational direction and support for working within regulations to expedite the development and delivery of safety and efficacy in pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines, healthcare products to individuals around the world. Regulatory affairs (RA) professionals are employed in pharmaceutical industry, government, academic research and clinical institutions. As India is growing very rapidly in pharmaceutical sector, there is a need of regulatory affairs professionals to cater the current needs of industries for the global competition. Regulatory affairs professionals are the link between pharmaceutical industries and worldwide regulatory agencies. A regulatory affair is a somewhat new

profession which has developed from the desire of governments to defend public health. Substantial documentation and data are required in these types of submissions, resulting in large, complex applications. Today 35 member countries along with 11 candidate countries and 4 international agencies have joined together to create the Pharmaceutical Inspection Cooperation Scheme (PIC/S) to promote a globally accepted GMP.

**KEYWORDS:** Drug regulatory affairs, Regulatory agencies, FDA, Pharmaceutical Inspection Cooperation Scheme (PIC/S), GMP.

## INTRODUCTION

Regulatory affairs is a vast field to study. It takes a several years for a professional to comprehend a small segment of this field. Through the dynamics of RA firms assure regulatory agencies that the products marketed meet all the regulatory expectations in regards to quality, purity, safety and efficacy. The complexity of regulatory affairs is several folds magnified when a drug, device or biological product manufacturer exporting to several countries.

RA involves complex dynamics-

- Multi-dimensional
- Knowledge in science and technology
- Prolific communication skill
- Deal with people with diverse backgrounds, skills cultures and personalities
- Deal with conflicting loyalties, motivations, social and ethical responsibilities<sup>[2]</sup>

The current Pharmaceutical Industry is well organized, systematic and compliant 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. Stringent GMPs are being followed for blood and its derivative as well as controlled manufacturing for Traditional Herbal Medicines, Cosmetics, Food and Dietary products which was otherwise differently a century before. 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.

During 1950s, multiple tragedies i.e. sulfanilamide elixir, vaccine tragedy and thalidomide tragedy have resulted in substantial increase of legislations for drug products quality, safety and efficacy. This has also resulted into stricter norms for Marketing Authorization (MA) and Good Manufacturing Practices (GMPs). One of the vital activities of the regulatory authority is to ensure that the all the information regarding medicines has been correctly established to the patient covering labeling also. Even a small mistake in any of the activities related to regulatory can make the product to be recall in addition to loss of several millions of the money.<sup>[3]</sup>

## IMPORTANCE OF REGULATORY AFFAIR

The importance of the Regulatory Affairs function is such that senior Regulatory Affairs professionals are increasingly being appointed to boardroom positions, where they can advise upon and further influence the strategic decisions of their companies. A good Regulatory Affairs professional will have a 'right first time' approach and will play a very important part in coordinating scientific Endeavour with regulatory demands throughout the life of the product, helping to maximize the cost-effective use of the company's resources. A new drug may have cost many millions of Euros or dollars, pounds, to develop and even a three- month delay in bringing it to the market has considerable financial considerations. Even worse, failures to fully report all the available data or the release of product bearing incorrect labeling, may easily result in the need for a product recall. Either occurrence may lead to the loss of several millions of units of sales, not to mention the resulting reduction in confidence of the investors, health professionals and patients. The Regulatory Affairs department is very often the first point of contact between the government authorities and the company.<sup>[1]</sup>

## 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 of 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.<sup>[1]</sup>

## LEGISLATIVE HISTORY OF DRUG REGULATION

Derived from the Dutch word meaning *to boast (quacken)*, “quack” is the word Americans have commonly used to describe charlatans in medicine. Quacks peddled adulterated and mislabeled medicines throughout the United States without penalty until 1906, when Congress passed the Food and Drugs Act, one section of which outlawed the practice. Over the next half-century, Congress passed two major pieces of legislation expanding FDA authority. It passed the Federal Food, Drug, and Cosmetic Act (FFDCA) in 1938, requiring that drugs be proven safe before they could be sold in interstate commerce. Then, in 1962, in the wake of deaths and birth defects from the tranquilizer thalidomide marketed in Europe, Congress passed the Kefauver-Harris Drug Amendments to the FFDCA, increasing safety provisions and requiring that drugs be proven effective as well. Congress has amended the FFDCA many times, leading to FDA’s current mission of assuring Americans that the medicines they use do no harm and actually work—that they are.

Information is often described as the currency of the 21st century, and for RA this has been the case since the earliest days of the profession. Regulatory is the interface between the company/sponsor and the outside world (in terms of regulators/regulatory authorities). As a conduit or a funnel, the regulatory department is a focal point of information, both incoming and outgoing. In order to practice regulatory and succeed, both in objective public measures (e.g., approvals) and internal ones (e.g., recognition and reward), recognizing the power of information and learning to manage it is gathering Information.<sup>[2]</sup>

## REGULATORY AFFAIRS IN PRODUCT MANAGEMENT<sup>[4]</sup>

The key role of RA professional is broader than registration of products, they advise companies both strategically and technically at the highest level. Their role begins right from development of a product to making, marketing and post marketing strategies. Their advice at all stages both in terms of legal and technical requirements help companies save a lot of time and money in developing the product and marketing the same. For countries that do not have their own regulations the World Health Organization guidelines on health matters and World Trade Organization on trade regulations between nations is followed.

## REGULATORY AFFAIRS IN CLINICAL TRIALS<sup>[4]</sup>

The RA professional is the primary link between the company and worldwide regulatory agencies such as US Food and Drug Administration (USFDA & Center for Devices and Radiological Health) Medicines and Healthcare Products Regulatory Agency, United

Kingdom, (UKMCA), Therapeutic Goods Administration, Australia European Medicines Agency, Organization of Economic Collaboration and Development (OECD) and Health Canada. He also communicates and interprets the seemingly endless mace of laws, regulations and guidelines to the other departments of the company. The RA personnel develops strategies to overcome delays and presents finding of clinical trials to the regulatory bodies so as to get quick clearance thus reducing the time for approval of new molecules. At its core, the RA professional facilitates the collection, analysis and communication about the risks and benefits of health products to the regulatory agencies, medical and health systems and the public. Operationally RA is responsible for assuring that government obligation, market driven demands and evolving scientific conventions are understood and addressed by various stakeholders.

### REGULATORY AFFAIRS IN R&D<sup>[4]</sup>

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.

### REGULATORY BODIES IN DIFFERENT COUNTRIES<sup>[5]</sup>

Country	Regulatory Authority	
India	CDSCO	Central Drugs Standard Control Organization
Europe	EDQM, EMEA	European Directorate for Quality of Medicines, European Medicines Evaluation Agencies.
UK	MHRA	Medicines and Health care products Regulatory Agency.
Australia	TGA	Therapeutic Goods Administration.
Japan	MHLW	Japanese Ministry of health, Labour and Welfare.
Canada	HC	Health Canada
Brazil	ANVISA	Agency Nacional degradation Vigilancia Sanitaria
South Africa	MCC	Medicines Control Council.
USA	FDA	Food and Drug Administration.

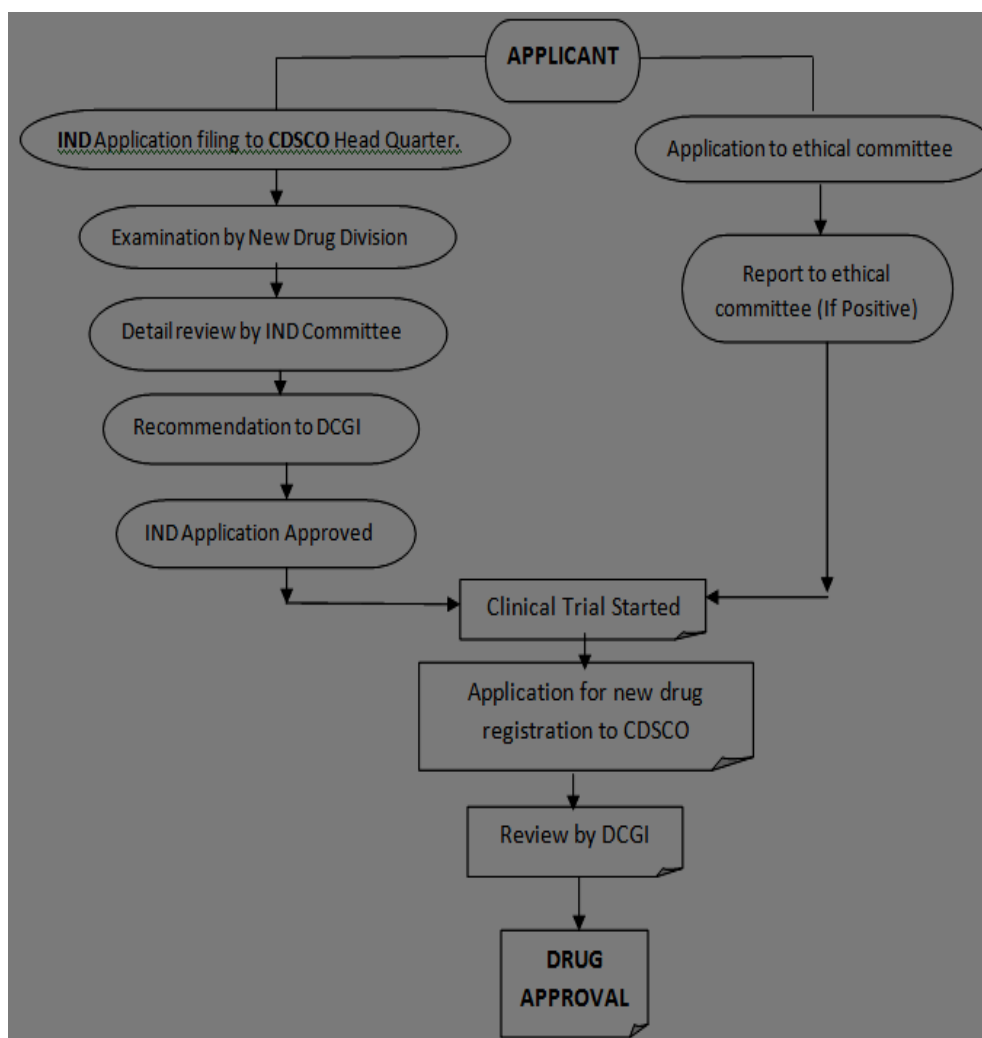
**REGULATORY APPROVAL & SUBMISSION PROCEDURE IN INDIA<sup>[6]</sup>**

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.

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. The changes includes, establishing definitions for Phase I–IV trials and clear responsibilities for investigators and sponsors. The clinical trials were further divided into two categories in 2006. In one category (category A) clinical trials can be conducted in other markets with competent and mature regulatory systems whereas the remaining ones fall in to another category (category B) Other than A. Clinical trials of category A (approved in the U.S., Britain, Switzerland, Australia, Canada, Germany, South Africa, Japan and European Union) are eligible for fast tracking in India, and are likely to be approved within eight weeks. The clinical trials of category B are under more scrutiny, and approve within 16 to 18 weeks. An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI. The data regarding the trial protocol, investigator's brochures, and informed consent documents should also be attached. A copy of the application must be submitted to the ethical committee and the clinical trials are conducted only after approval of DCGI and ethical committee. To determine the maximum tolerated dose in humans, adverse reactions, etc. on healthy human volunteers, Phase I clinical trials are conducted. The therapeutic uses and effective dose ranges are determined in Phase II trials in 10-12 patients at each dose level. The confirmatory trials (Phase III) are conducted to generate data regarding the efficacy and safety of the drug in ~ 100 patients (in 3- 4 centers) to confirm efficacy and safety claims. Phase III trials should be conducted on a minimum of 500 patients spread across 10-15 centers, if the new drug substance is not marketed in any other country. The new drug registration (using form number 44 along with full preclinical and clinical testing information) is applied after the completion of clinical trials. The comprehensive information on the marketing status of the drug in other countries is also required other than the information on safety and efficacy. The information regarding the prescription, samples and testing protocols, product monograph, labels, and cartons must also be submitted. The application can be reviewed in a range of

about 12-18 months. Figure 10 represents the new drug approval process of India. After the NDA approval, when a company is allowed to distribute and market the product, it is considered to be in Phase IV trials, in which new uses or new populations, long-term effects, etc. are explored. The drug approval process varies from one country to another. In some countries, only a single body regulates the drugs and responsible for all regulatory task such as approval of new drugs, providing license for manufacturing and inspection of manufacturing plants e.g. in USA, FDA performs all the functions. However in some countries all tasks are not performed by a single regulatory authority, such as in India, this responsibility is divided on Centralized and State authorities. Other issues where the difference appears are, time taken for the approval of a CTA application, time taken in evaluation of marketing authorization application, registration fee, registration process and marketing exclusivity. Some countries have two review processes as normal review process and accelerated review process as in USA, China etc. and some countries have only a single review process as in India. Similarly, the format used for the presentation of dossier submitted for approval of drug is also different. In some countries like as in USA, EU, and Japan, it is mandatory that the dossier prepared in CTD format, however, in some countries it is optional such as in India.

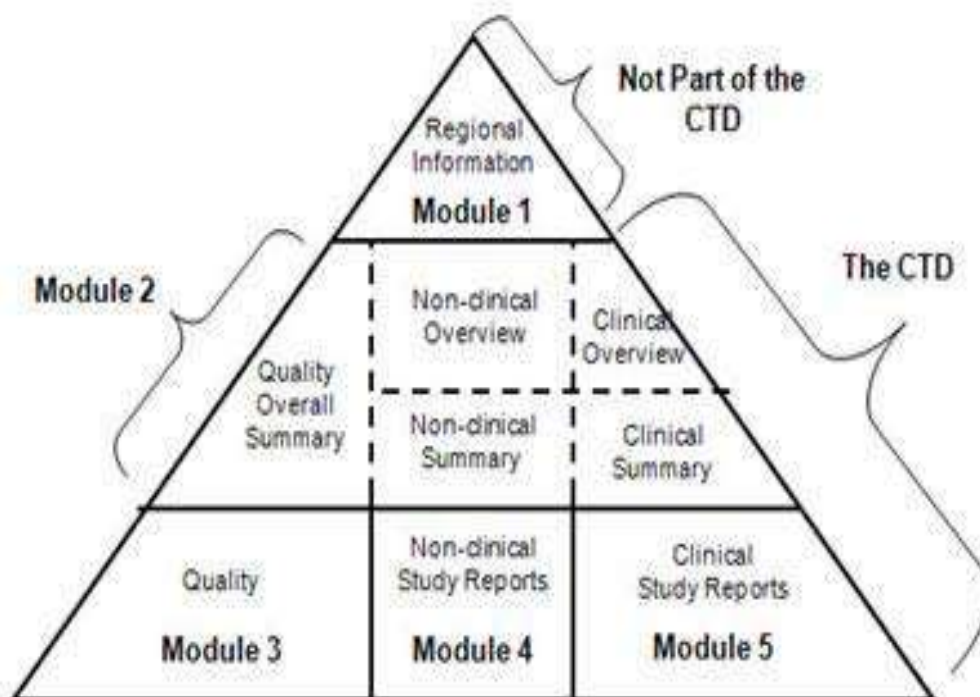




### COMMON TECHNICAL DOCUMENTS (DOSSIER)<sup>[7],[8]</sup>

Dossier is a file document submitted for the approval of new drug or drug product. It is submitted in form of CTD. CTD is a harmonized format (template) for presenting data in the ICH regions. In some country it is optional. The process of reviewing & assessing dossier to support a medicinal product in view of its marketing (also called licensing, registration, approval, etc.), obviously finalized by granting of a document also called marketing authorization. This process is performed within a legislative framework which defines the requirements necessary for application to the concerned (competent) regulatory authority, details on the assessment procedure (based on quality, efficacy and safety criteria) and the grounds for approval or rejection of the application, and also the circumstances where a marketing authorization already granted may be withdrawn, suspended or revoked. CTD format intends to harmonize the structure and format of registration documentation. Benefits Complete, well-organized submissions, facilitates electronic submissions, easier analysis across applications etc.





### The CTD is organized into five modules

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

#### Module 1.

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

1.1 Table of Contents

1.2 Documents Specific to Each Region (for example, application forms, prescribing information,)

#### Module 2.

CTD Summaries Begin with a general introduction to the pharmaceutical (its pharmacological class, mode of action, proposed clinical use. It contains 7 sections in the following order.

2.1 Common Technical Document Table of Contents

(Modules 2-5)

2.2 CTD Introduction

### 2.3 Quality Overall Summary

### 2.4 Non-clinical Overview

### 2.5 Clinical Overview

### 2.6 Non-clinical Written and Tabulated Summaries

### 2.7 Clinical Summary

## **Module 3. Quality**

### 3.1 Table of Contents of Module 3

### 3.2 Body of Data [Drug Substance, Drug Product & Regional information]

### 3.3 Literature References

## **Module 4. Non clinical / preclinical study reports**

### 4.1 Table of Contents of Module 4

### 4.2 Study Reports

### 4.3 Literature References

## **Module 5. Clinical Study Reports**

### 5.1 Table of Contents of Module 5

### 5.2 Tabular Listing of All Clinical Studies

### 5.3 Clinical Study Reports (BA/BE)

### 5.4 Literature References.

## **CONCLUSION**

Regulatory Affairs department is constantly evolving and growing and is the one which is least impacted during the Acquisition and Merger, and also during recession. Regulatory Affairs departments are growing within companies. Due to the changing resources necessary to fulfill the regulatory requirements, some companies also choose to outsource or out task regulatory affairs to external service providers. In today's competitive environment the reduction of the time taken to reach the market is critical to a product's and hence the company's success. The proper conduct of its Regulatory Affairs activities is therefore of considerable economic importance for the company. CTD and eCTD significantly reduces the time and resources needed to compile applications for registration of human pharmaceuticals. Eases the preparation of electronic submissions.

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