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A REVIEW ON REGULATORY AFFAIRS

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ABSTRACT

Regulatory affairs in pharmaceutical industry aim at the protection of human health . People and government spent money on drugs because of the role they can play in saving lives , restoring health , preventing diseases and stopping epidemics . But , in order to do so , drug must be safe , effective and of good quality . Since the purpose of drug is to diagnose , prevent or treat diseases or ailments in humans, they are products intimately linked with the advances in research and regulation . The pharmaceutical industry , while pursuing an international market , is obliged to comply with national regulations . So , in this review article , a review on regulatory affairs is covered . Regulatory agencies and organizations play a vital role to meet the requirements of legal procedures related to drug development process in a country . Every country has its own regulatory authority , which is responsible to enforce the rules and regulations and issue the guidelines to regulate the drug development , licencing & registration .

Regulatory affairs professional play significant roles in the pharmaceutical industry as it concerns the lifecycle of the healthcare product, it offers operational direction, tactical and strategic, and assistance for working within the regulation to accelerate development as well as distribution of healthcare products safe and efficient to expedite the development role of regulatory affairs, a regulatory strategy is developed and implemented, to guarantee that the collective actions of the team of drug development lead to products which are approved by the Global Regulator but is also differentiated in certain ways from the competition and is also to assure promotion, are carried out in according to the guidelines and regulation founded by a regulatory authority. Regulatory affairs (RA) are an interesting career option for science graduate students who enjoy communication and teamwork, comfort with multi-task, and want to develop their knowledge in the broader area of the pharmaceutical sector. RA is a rewarding, intellectually stimulating, as well as highly respected profession in a pharmaceutical company.

Keywords*: Regulatory Agencies, Regulatory Affairs Professionals, Regulatory Bodies, Regulatory Affairs, Pharmaceutical Industries, Regulatory Requirements, Registration Process, Drug Approval.*

1. 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. [1]

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.[2]

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.[3]Drug Development is long, risky, expensive, and these characteristics mean regulatory affairs has forceful emphasis to improve safety, efficacy, quality of the medicinal product. A new drug molecule can cost several millions of rupees or dollars to progress 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.[4]

The regulatory affairs authorities are the only one who is completely responsible for holding products in compliance and maintaining all the records. So for the same purpose regulatory bodies given emphasis on the origin of the product and its requirement, preclinical studies, formulation and development, clinical studies as phase I to phase IV.[5] 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.[6]

Drug development to commercialization is highly regulated. Every drug before getting market approval must undergo rigorous scrutiny and clinical trials to ensure its safety, efficacy and quality. These standards are set by regulatory authorities of their respective countries such as FDA in US and DCA in India etc. Regulation affects all aspects of the pharmaceutical world, from independent innovators and pharmaceutical companies to regulatory and administrative bodies and patients also. Regulatory department in pharmaceutical industry is crucial link between company, products and

regulatory authorities whose positive or negative standpoint 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.

Regulatory importance is growing very rapidly in the pharmaceutical sector; need of PRA professionals to cater to the current needs of industries globally is increasing. Pharmaceutical industry is in immense need of professionals capable of handling issues related to regulatory affairs in a comprehensive manner. MNCs abroad are looking to India as their preferred destination for drug development, research activities and contract research organizations. A regulatory affair is a dynamic, rewarding field that embraces both scientific and legal aspects of drug development; plays a lead and pivotal role in drug development and research activities. There is a need to incorporate the current requirements of pharmaceutical updates incorporated by the regulatory bodies.[6]

Regulation involves extensive evaluation of a particular drug product to ensure protection of public health, promotion of the product, Drug registration, marketing authorization, import and distribution, pharmacovigilance. Regulatory Affairs is a comparatively new profession which has developed from the desire of governments to protect public health, by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines.

2. DEFINITION

Regulatory Affairs (RA), also called Government Affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory Affairs also has a very specific meaning within healthcare industries (pharmaceuticals, medical devices, Biologics and functional foods) [7]. Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory Affairs [8].

Definition according to Swedish Pharmaceutical Society: Regulatory Affairs is the knowledge and application of strategic and operational enforcement of the legal frame work concerning pharmaceuticals and related products in a national and global perspective.

Regulatory affairs professionals usually have responsibility for the following general areas:

- 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. i.e. working with such agencies as the Food and Drug Administration or European Medicines Agency
- Advising their companies on the regulatory aspects and climate that would affect proposed activities. i.e. describing the "regulatory climate"…
- **Company perspective:** New medicinal products - and changes to marketed products – should be approved asap and placed and kept on the market
- **Authority perspective:** To assess documentation submitted with the registration- or change application and surveillance of the use of medicinal products

3. HISTORICAL BACKGROUND OF REGULATORY AFFAIRS

In 1950's, multiple tragedies such as the sulfanilamide elixir, vaccine tragedy, and thalidomide tragedy have resulted in a substantial increase of the legislations for drug products quality, safety and efficacy. This has also resulted into stricter norms for marketing authorization and good manufacturing practices. In 1937 due to diethylene glycol poisoning, 100 people died and in 1956 a thalidomide disaster which majorly triggered for the development of the modern regulatory controls on the drug development and supply. [9] Hence to ensure the quality, safety 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.

4. 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.[10]

5. SCOPE OF REGULATORY AFFAIRS PROFESSIONALS

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.

RA professionals are used in academics government regulatory bodies as well as industry. In these domains there are a broad variety of regulatory professionals:

- Biologics and Biotechnology
- Cosmetics
- In-vitro diagnostics
- Medical devices
- Nutritional Products
- Pharmaceuticals
- Veterinary Products

Importance and need of Regulatory Affairs:

- All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy
- To ensure quality, safety and efficacy of drug products in order to assure the continued protection of Public Health.
- 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. Benefits versus risks.

A new drug may involve a huge investment in its development and thus a few months delay in reaching it to the market may require enormous financial consideration. In worst cases, failure to completely provide all relevant data or to disclose the inaccurate labelling of the product might simply lead to the recall of the product. Either of these issues could result in the loss of several million sales units, and most importantly the decrease in confidence of the investor, patients as well as health professionals. RA is the initial point of connection between the government agency and the corporation. [11]

Qualities of Regulatory Affairs Professionals:

The main role of the DRA professional within a pharmaceutical Industry is to secure approval of drug submissions from Health Therapeutic Products Program and to ensure regulatory compliance of marketed and investigational drugs with the Food and Drug Act and Regulations and Guidelines/Policies.

The DRA professional must actively participate in discussions and coordinate team activities to obtain all the necessary documentation and then assess it for completeness and accuracy. Therefore, an effective DRA professional must exhibit the organizational and interpersonal skills of a "team player" and also be thorough and detail oriented.

The scope of responsibilities is so wide and may vary significantly according to the organizational structure of the pharmaceutical company. The responsibilities of some DRA professionals may focus on Pharmacovigilance activities or on the electronic representation of data (electronic submissions). Other responsibilities may include product launch activities, DMF submission, formulary submissions, review of advertising materials and quality assurance. The primary function is the liaison between the Ministry of Health & Company.

Skills & Attributes required for making a good RA Skills

- Influence IT Literate
- Work independently
- Persuade Accuracy
- An effective negotiator
- Present Quality
- Excellent writing and communication skills
- Listen actively

- Interpret and consolidate data
- Strong follow-ups and convincing ability
- Technical sound knowledge

Responsibilities of Regulatory Affairs Department:

Regulatory affairs (RA) professionals help the company avoid problems caused by badly kept records, inappropriate scientific thinking or poor presentation of data. In most product areas where regulatory requirements are imposed, restrictions are also placed upon the claims which can be made for the product on labelling or in advertising. [12]

List of responsibilities of Regulatory Affairs Department:

1. Keep in touch with international legislation, guidelines and customer practices

2. Keep up to the date with a company's product range

3. Ensure that a company's products comply with the current regulations.

4. The Regulatory Affairs professional's job is to keep track of the ever-changing legislation in all the regions in which the company wishes to distribute its products. They also advise on the legal and scientific restraints and requirements, and collect, collate, and evaluate the scientific data that their research and development colleagues are generating.

5. Formulate regulatory strategy for all appropriate regulatory submissions for domestic, international and/or contract projects.

6. Coordinate, prepare and review all appropriate documents for example dossier and submit them to regulatory authorities within a specified time frame in conjugation with the organization.

7. Prepare and review of SOPs related to RA. Review of BMR, MFR, change control and other relevant documents.

8. Monitor the progress of all registration submission.

9. Maintain approved applications and the record of registration fees paid against submission of DMF's and other documents.

10. Respond to queries as they arise, and ensure that registration/ approval are granted without delay. [13]

11. Impart training to R&D, Pilot plant, ADl and RA. Team members on current regulatory requirements.

Roles of Regulatory Affairs Professional:

This department is responsible for knowing the regulatory requirements for getting new products approved. They know what commitments the company has made to the regulatory agencies where the product has been approved. They also submit annual reports and supplements to the agencies. Regulatory Affairs is a comparatively new profession which has developed from the desire of governments to protect public health, by controlling the safety and efficacy of products in areas including pharmaceuticals, veterinary medicines, medical devices, pesticides, agrochemicals, cosmetics and complementary medicines. [14]

The role of regulatory affairs professional is to act as liaison with regulatory agencies. Preparation of organized and Ensure adherence and compliance with all the applicable CGMP, ICH, GCP, GLP guidelines regulations and laws. They are providing expertise and regulatory intelligence in translating regulatory requirements into practical, workable plans. A regulatory affair plays a crucial role in the industry and is involved in all stages of drug development and also after drug approval and marketing. Pharmaceutical companies use all the data that has been observed during the discovery and development stages to register the drug and thus market the drug. Throughout the development stages, pharmaceutical companies have to follow the strict rule and guidelines to ensure the safety and efficacy of the drug in humans.

Regulatory Affairs In The Pharmaceutical Industries:

Professionals from regulatory affairs provide technical as well as strategic guidance to R&D, production, departmental QC, etc., providing an essential scientific and commercial contribution to the success of a product development program as well as the corporation as an entirety. A new pharmaceutical product takes up to fifteen years to develop and commercialize, and there might be various obstacles in the scientific development process as well as a varying regulatory environment.

- **Regulatory Affairs In Product Management:**

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:**

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 Research & Development:**

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. [15]

Challenges to Regulatory Affairs Profession:

Regulatory affairs include complete dynamics:

- Multi –dimensional
- Knowledge in science and technology
- Prolific communication skill
- Deal with people with diverse background, skills, culture, and personalities
- Deal with conflicting loyalties, motivations, social and ethicals, responsibilities
- Case in point: submission of a dossier
- During submission of a dossier a regulatory affair would be:
- Guided by various regulatory guidance
- Receiving input from various department within the firm about process capabilities and product attribute specification
- Receiving advice from peers about easy way to get approvals
- Receiving motivation from the management through incentives for achieving speedy approvals

- **Regulatory challenges that involved in the development of a new drug and generics are as follows:**

1. Generics:
   Bioequivalence is the major regulatory challenge for the development of a new generic.
2. Patent expiries:
   The second major regulatory challenge is patent and intellectual property rights. In US the patent and trademark office is the regulatory agency that grants patents which permit the patent holder to assert their rights to exclude others from making, using or selling the patented invention or process.
3. Newer antibiotics:
   In contrast to the earlier times only penicillin was the available antibiotic in the market, several hundreds of antibiotic started getting approval from the agency. As a result of 1962 Amendments, the FDA required the submission for several antibiotics of scientific evidence of substantial well controlled clinical studies demonstrating the effectiveness of the product; In contrast to the earlier those product that failed to provide such evidence had their certifications overturned. In addition, the FDA cancelled approval of several antibiotics that did not have substantial scientific evidence.
4. Clinical trials:
   FDA regulations that specify methods for clinical trials requires each new drug application to include data from at least two controlled clinical trials.
5. Consumer risks:
   Regulatory environment for drugs and the spectrum of indications for which they will be approved and marketed would change dramatically if positive data from either the SCOUT or CRESCENDO outcome trials.
6. Medical devices:

Since the beginning of 1980s, the regulatory world for medical has changed dramatically. From few countries, there are now 60-65 countries which have implemented regulations for medical devices.

Product Life Cycle – RA Perspective:

- **Development Phase**

  - Advice on development
  - Scientific Advice
  - Clinical Trial Applications
  - Project management / Strategy
  - Product Information – Claims

- **Application and Approval Phase**

  - Application Procedure
  - Authority meetings/hearings
  - Electronic submission
  - Readability Testing / Labeling Support

- **Post Approval Phase**

  - Life Cycle
  - Management/Compliance
  - Post-approval Commitments
  - Clinical Trial Applications
  - New Indications

INTERNATIONAL ORGANIZATIONS:

Table 1: Different regulatory bodies in World [16]

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

REGULATORY APPROVAL & SUBMISSION PROCEDURE IN INDIA:

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. [17]

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. [18]

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 date 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. [18] 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. [18]

The new drug registration (using form number 44 along with full pre-clinical 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. [19]

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 counties 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 counties 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.

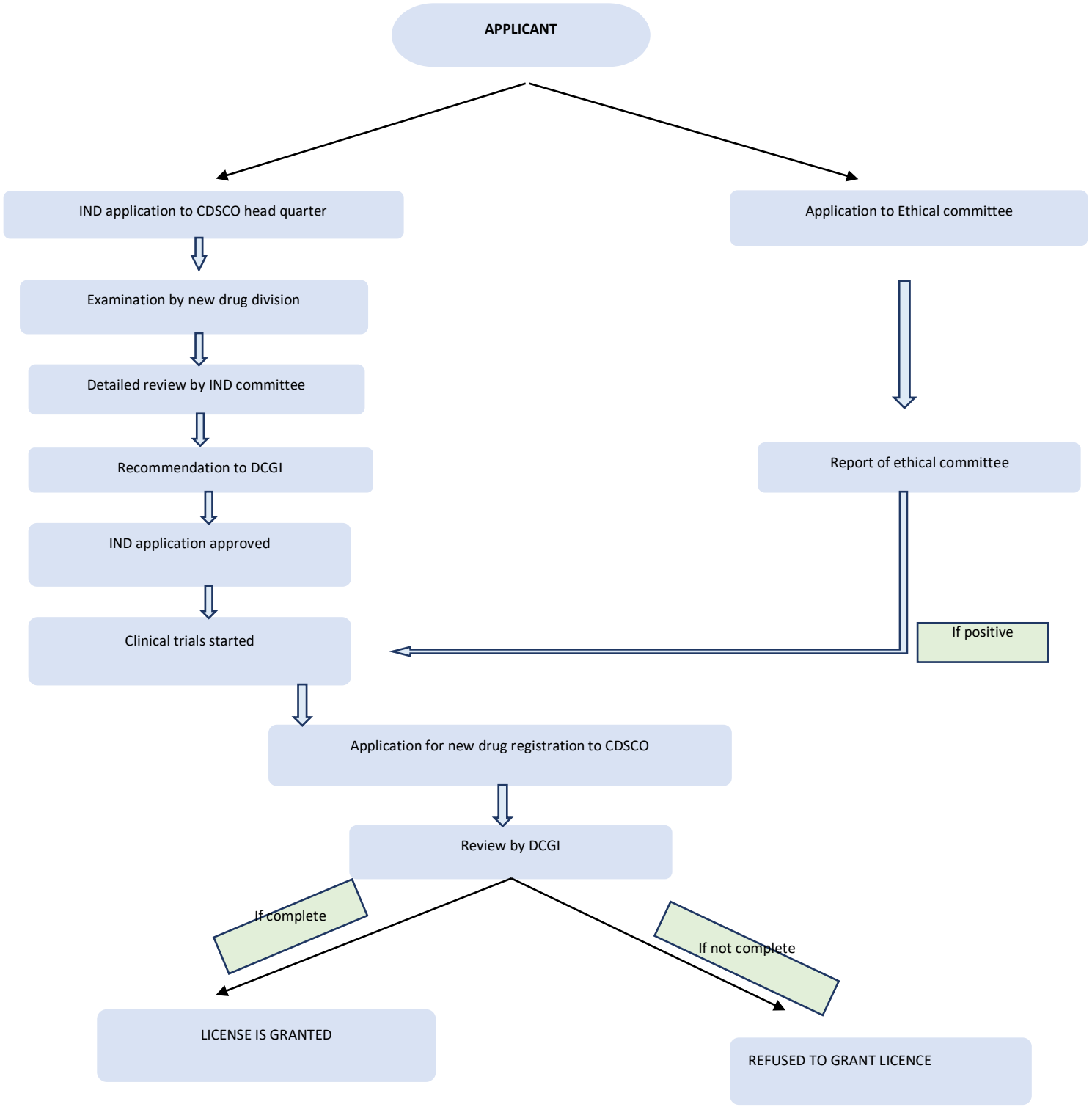

FIG 1: DRUG APPROVAL PROCESS IN INDIA

Regulatory guidelines for dossier submission in India:

The following regulatory authorities run in India for the drug discovery, development and approval process.

CDSCO: A licensing authority for approval of new drug proposed to be imported Head office located in New Delhi & functioning under the control of directorate general of Health services, MHFW, Govt of India. [20]

DCGI: Responsible for approval of new drug & Clinical trials to be conducted in India Appointed by Central Govt. of India.

Drug & Cosmetic Act 1940 & Rules 1945: Regulates the import, manufacture, distribution & sale of drugs & cosmetics.

Schedule Y: Provides guidelines & requirements for clinical trials.

RECENT ADVANCEMENT IN DRUG REGULATORY AFFAIRS:

Recently, the Govt. of India has constituted a few autonomous bodies to gauge the standards of profession of Pharmacy & grade the colleges accordingly so that the students, parents, employers and funding agencies have a valid & reliable rating of the various Pharmacy colleges in the country.[21]

These are:

1) National Board of Accreditation (NBA) under the aegis of All India Council for Technical Education.

2) National Assessment and Accreditation Council (NAAC) by the UniversiEducation Commission

6. CONCLUSION

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. Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of Regulatory affairs professionals and Regulatory affairs department is constantly evolving the one which is least impacted during the acquisition and merger, and also during recession. 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 within the company's for their success and growth. The proper conduct of its Regulatory Affairs activities is therefore of considerable economic importance for the company.

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