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Review Article

REGULATORY REQUIREMENTS AND APPROVAL PROCESS OF NEW DRUG IN INDIA AND USA

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ABSTRACT

A regulatory process is by which a person/organization/sponsor/innovator gets authorization to launch a drug products in the particular market region by following respective regulatory guidelines. Developing a new drug requires great amount of research work in chemistry, manufacturing, controls, preclinical sciences and clinical trials. Drug reviewers in regulatory agencies around the world bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of new drug product to serve the public health. In general, a drug approval process comprises of various stages: application to conduct clinical trials, application to marketing authorization of drug and post-marketing studies. Every country has its own regulatory authority, which is responsible to enforce the rules and regulations and issue the guidelines to regulate the marketing of the drugs. In the present scenario, different countries have to follow different regulatory requirements for Marketing Authorization Application (MAA) approval of new drug. In this article, we studied the new drug approval process and regulatory requirements in India and US according to their regulatory agencies.

Keywords: Central Drugs Standard Control Organization (CDSCO), United States of Food and Drug Administration (USFDA), NewDrug Approval,Marketing Authorization Application (MAA).

1. INTRODUCTION [1]

The new drug approval is of two phase process - the first phase for clinical trials and second phase for marketing authorization of drug. Firstly, non-clinical studies of a drug are completed to ensure efficacy and safety, and then application for conduct of clinical trials is submitted to the competent authority of the concerned country. Thereafter, the clinical trials can be conducted (phase I to phase IV). These studies are performed to ensure the efficacy, safety and optimizing the dose of drug in human beings. After the completion of clinical studies of the drug, then an application to the competent authority of the concerned country for the approval of drug for marketing is submitted. The competent authority review the application and approve the drug for marketing only if the drug is found to be safe and effective in human being or the drug have more desirable effect as compare to the adverse effect.

Even after the approval of new drug, government should monitor its safety due to appearance of some side effects, when it is used in larger population. The interactions with other drugs, which were not assessed in a pre-marketing research trial and its adverse effects (in particular population) should also be monitored.

Currently different countries have to follow different regulatory requirements for approval of new drug. For marketing authorization application (MAA) a single regulatory approach is applicable to various countries is almost a difficult task. Therefore it is necessary to have knowledge about regulatory requirement for Marketing Authorization Application of each country. The basic regulations for the new drug approval can be understood from fig. 1.

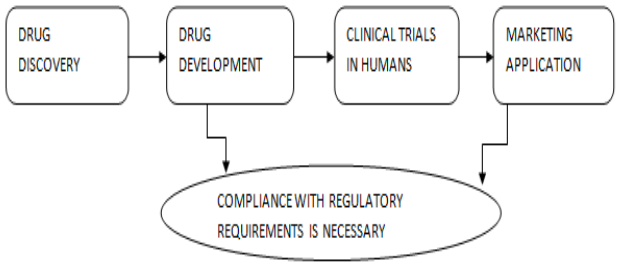

Fig. 1: Regulation of Drug Approval Process

2. REGULATIONS OF DRUG APPROVAL PROCESS [2,3]

New Drug Application (NDA) is an application submitted to the respective regulatory authority for

permission to market a new drug [2]. To obtain this permission a sponsor submits preclinical and clinical test data for analyzing the drug information, description of manufacturing procedures. Different Phases of clinical trials:

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

After NDA received by the agency, it undergoes a technical screening. This evaluation ensures that sufficient data and information have been submitted in each area to justify "filing" the application.

At the conclusion of the review of an NDA, there are 3 possible actions that can send to sponsor:

- Not approvable- in this letter list of deficiencies and explain the reason.
- Approvable - it means that the drug can be approved but minor deficiencies that can be corrected like-labeling changes and possible request commitment to do post-approval studies.
- Approval- it state that the drug is approved.

If the action taken is either an approvable or a not approvable, then the regulatory body provides applicant with an opportunity to meet with agency and discuss the deficiencies.

3. PROCEDURE FOR NEW DRUG APPROVAL 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] were established [4].

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 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. 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 # 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 [5].

The application can be reviewed in a range of about 12-18 months. 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 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 [4, 5].

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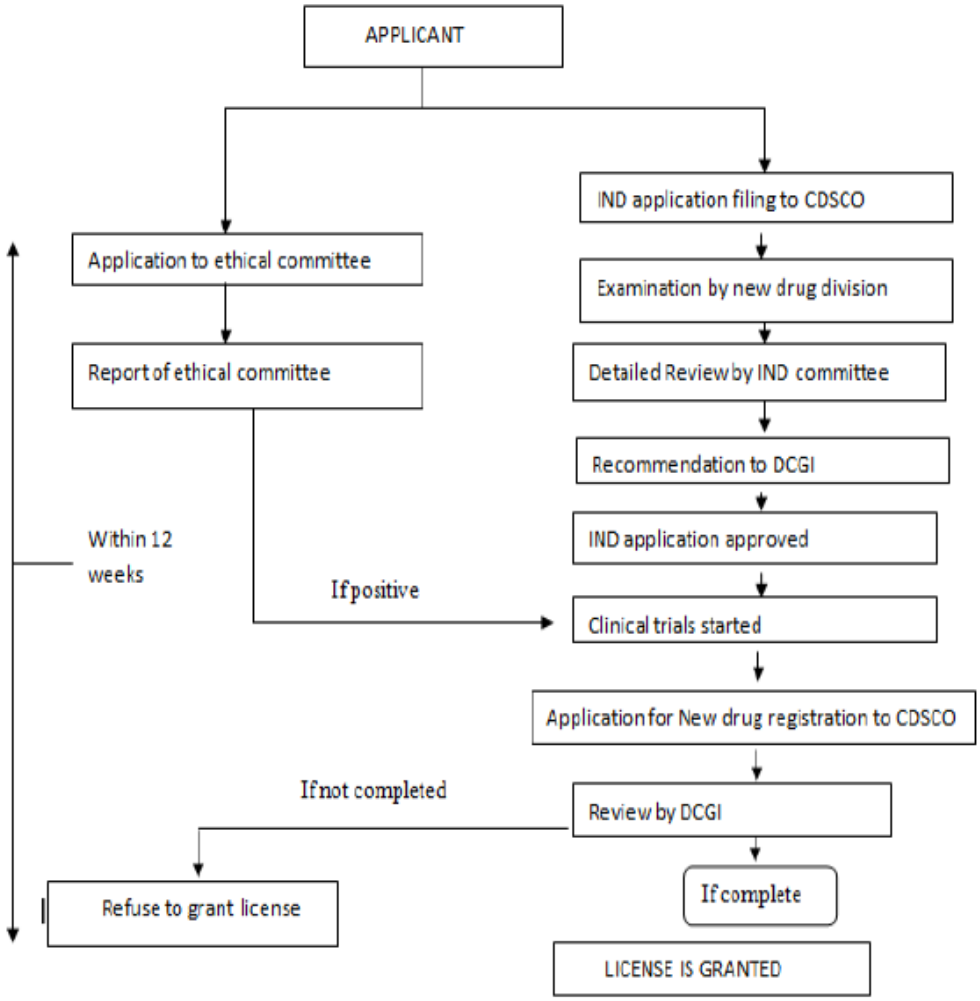

Fig. 2: Drug approval process in INDIA

3.1. Timelines for NDA [6]

Country	Time for regulatory approval of CTA/IND application	Time for evaluation of MAA	MAA fees
India	16-18 weeks	8-12 weeks	50000 INR

3.2. Drug Approval Stages in India

	Clinical Trials								
	Preclinical testing		**Phase I**	**Phase II**	**Phase III**		**FDA**		**Phase IV**
Years	3.5		1	2	3		2.5	12 total	**Additional Post marketing testing required by FDA**
Test Population	Laboratory and animal studies	File IND at FDA	20- 80 Healthy volunteer	100-300 patient volunteers	1000-3000 patient volunteers	File NDA at FDA	Review process / Approval		
Purpose	Assess safety and biological activity		determine safety and dosage						
Success Rate	5,000 compounds evaluated		5 enter trials				1 approved		

4. DRUG APPROVAL PROCESS IN UNITED STATES [7, 8]

In 1820, the new era of USA drug regulation was started with the establishment of U.S. Pharmacopoeia. In 1906, Congress passed the original Food and Drugs Act, which require that drugs must meet official standards of strength and purity. However, in 1937, due to sulphanilamide tragedy, the Federal Food, Drug and Cosmetic Act (of 1938) was enacted and added new provisions that new drugs must be shown safe before marketing. Further, in 1962, the Kefauver-Harris Amendment Act was passed which require that manufacturers must prove that drug is safe and effective (for the claims made in labeling).

The Food and Drug Administration (FDA) is responsible for protecting and promoting public health. Like general drug approval process, FDA's new drug approval process is also accomplished in two phases: clinical trials (CT) and new drug application (NDA) approval. FDA approval process begins only after submission of investigational new drug (IND) application. The IND application should provide high quality preclinical data to justify the testing of the drug in humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed. The next step is phase-I clinical trials (1-3 years) on human subjects (~100).

The drug's safety profile and pharmacokinetics of drug are focused in this phase. Phase II trials (2 years) are performed if the drug successfully passes phase-I. To evaluate dosage, broad efficacy and additional safety in people (~300) are the main objective of the phase II. If evidence of effectiveness is shown in phase II, phase III studies (3-4 years) begins. These phase III concerns more about safety and effectiveness of drug from data of different populations, dosages and its combination with other drugs in several hundred to about 3,000 peoples [8, 9].

A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labeling. The preclinical, clinical reports and risk-benefit analysis (product's beneficial effects outweigh its possible harmful effects) are reviewed at the Center for Drug Evaluation and Research by a team of scientists. Generally approval of an NDA is granted within two years (on an average), however, this process can be completed from two months to several years. The

innovating company is allowed to market the drug after the approval of an NDA and is considered to be in Phase IV trials. In this phase, new areas, uses or new populations, long-term effects, and how participants respond to different dosages are explored. Fig. 1 represents the new drug approval process of FDA.

4.1. Investigational New Drug (IND) Application

It's an application filed to the FDA in order to start clinical trials in humans if the drug was found to be safe from the reports of Preclinical trials. A firm or institution, called a Sponsor, is responsible for submitting the IND application [4]. A pre - IND meeting can be arranged with the FDA to discuss a number of issues:

1. The design of animal research, which is required to lend support to the clinical studies
2. The intended protocol for conducting the clinical trial
3. The chemistry, manufacturing, and control of the investigational drug

Such a meeting will help the Sponsor to organize animal research, gather data, and design the clinical protocol based on suggestions by the FDA. Fig. 3 describes IND Approval Process in USA.

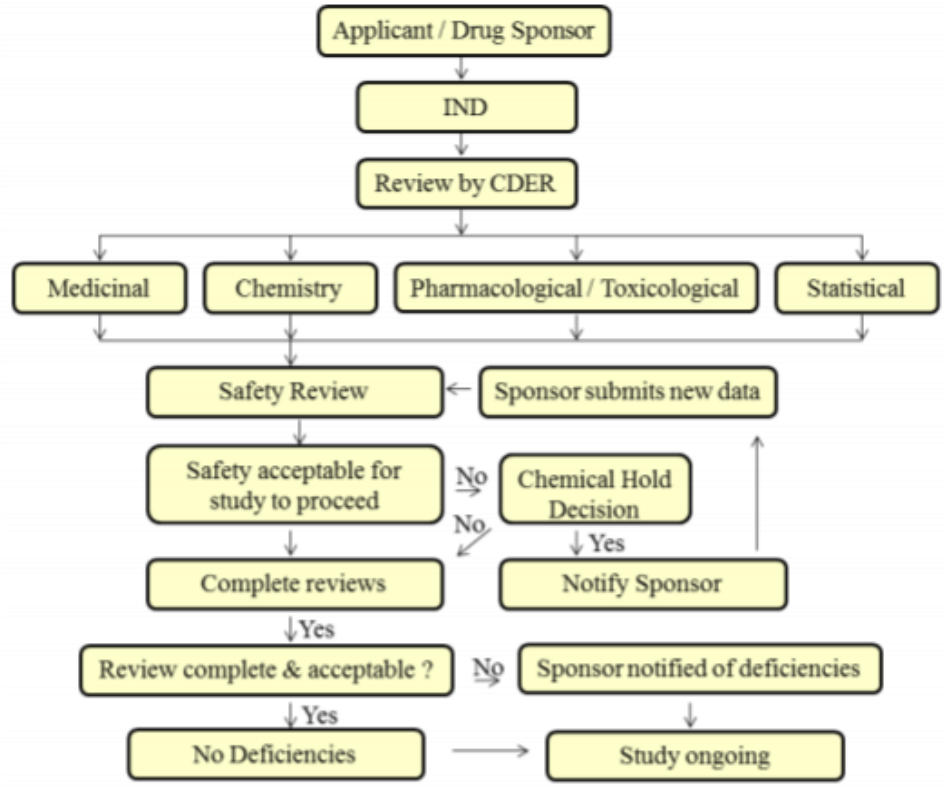

Fig. 3: Investigational New Drug Application Approval Process

4.2. New Drug Application (NDA)

The Food and Drug Administration's New Drug Application (NDA) is the vehicle in the United States through which drug sponsors formally propose that the FDA approve a new pharmaceutical for sale and marketing. Some 30% or less of initial drug candidates proceed through the entire multi-year process of drug development, concluding with an approved NDA, if successful [9].

The goals of the NDA are to provide enough information to permit FDA reviewers to establish the complete history of the candidate drug. Among facts needed for the application are:

- Patent and manufacturing information
- Drug safety and specific effectiveness for its proposed use(s) when used as directed
- Reports on the design, compliance, and conclusions of completed clinical trials by the Institutional Review Board
- Drug susceptibility to abuse
- Proposed labeling (package insert) and directions for use

The following are the two types of NDA:

- Traditional NDA (Section 505 (b) (1)
- Paper NDA (Section 505 (b) (2)

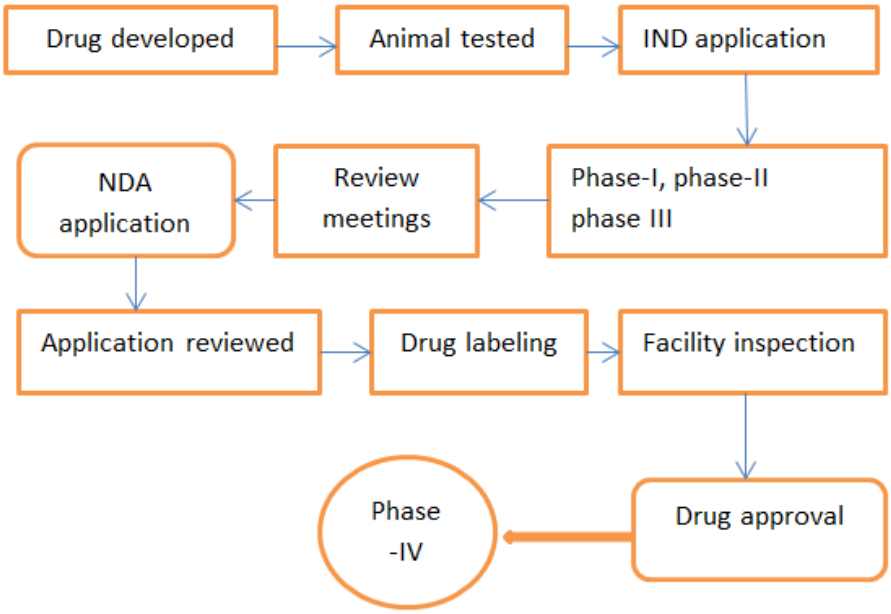

Fig. 4: New drug approval process in United States

5. DISCUSSION

Generally, the drug approval process comprised mainly the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug. The new drug approval process of various countries is similar in some of the aspects whereas it differs in some aspects [9, 10]. In most of the countries, sponsor firstly files an application to conduct clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is similar; however, the time, fee and review process of clinical trials and marketing authorization application differs. For the purpose of harmonization, the International Conference on Harmonization (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements. Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance has been developed for Japan, European Union, and United States. Hence, India also follows the same. This step will ultimately reduce the need to duplicate work carried out during the research and development of new drugs.

6. CONCLUSION

The Drug approval Process in the India is strictly controlled by the department of Central Drug Standards Control Organization (CDSCO) and in United States it's controlled by United States of Food and Drug Administration (USFDA). The primary purpose of the rules governing medicinal products in India and US is to safeguard public health. It is the role of public regulatory authority to ensure that pharmaceutical companies comply with regulations. There are legislations that require drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe and patient's well - being is protected.

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