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A COMPARATIVE STUDY OF DRUG APPROVAL PROCESS IN UNITED STATES, EUROPE AND INDIA

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ABSTRACT

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 CDSCO in India. A comparison of drug approval process requirements in US, Europe and India is discussed in this review article

KEYWORDS: Drug approval process, Regulatory affairs, US FDA, Europe, India, CDSCO.

INTRODUCTION

Developing a new drug requires great amount of research work in chemistry, molecular biology, biochemistry, preformulation and formulation development, process development and manufacturing, quality control, preclinical and clinical studies. Drug regulatory agencies globally bear the responsibility of evaluating whether the research data support the safety, effectiveness and quality control of a new drug product to serve the public health. 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. Different countries have different regulatory requirements for approval of new drug. For IND, NDA or marketing authorization application (MAA) a single regulatory approach applicable to various countries is almost a difficult task, not available at present. Therefore it is necessary to have knowledge about regulatory requirements for drug approval process of each country.

The new drug approval process consists of two stages, the first stage is for IND and the second stage is for NDA and marketing authorization of drug. Firstly, non-clinical studies of

drug are completed to ensure safety and efficacy. The next step is the submission of application for conduction of clinical trials to competent authority of respective country. In next step, clinical trials are carried out in four phases i.e. phase 1 to phase 4 study. These studies are carried out for the assurance of safety, efficacy and for optimization of dose of drug in human being. Then application for marketing of drug is varified by competent authorities. The competent authority review the application and approve the drug for marketing purpose, only if that drug is found to be safe and effective with desired therapeutic effect. The drug approval process in various countries is reviewed below.

Drug Approval Process in United States

The United States has the world's most stringent standards for approving new drugs. Drug approval standards in the United States are considered to be the most demanding in the world.[1-3]

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 like the design of animal research, which is required to lend support to the clinical studies, the intended protocol for conducting the clinical trial, 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.

New Drug Application (NDA)

If clinical studies confirm that a new drug is relatively safe and effective, and will not pose unreasonable risks to patients, the manufacturer files a New Drug Application (NDA), the actual request to manufacture and sell the drug in the United States.[5-6]

Abbreviated New Drug Application (ANDA)

It's an application made for approval of Generic Drugs. The sponsor is not required to reproduce the clinical studies that were done for the original, brand name product. Instead, generic drug manufacturers must demonstrate that their product is the same as, and bioequivalent to, a previously approved brand name product.[7]

An investigational new drug application (IND) outlines what the sponsor of a new drug proposes for human testing in clinical trials Phase 1 studies (typically involve 20-80 people) Phase 2 studies (typically involve a few dozen to about 300 people). Phase 3 studies (typically involve several hundred to about 3,000 people). The pre-NDA period, just before a new drug application (NDA) is submitted, is a common time for the FDA and drug sponsors to meet Submission of an NDA is the formal step the FDA takes to consider a drug for marketing approval 8. After an NDA is received, the FDA has 60 days to decide whether to file it so it can be reviewed 9. If the FDA files the NDA, an FDA review team is assigned to evaluate the sponsor's research on the drug's safety and effectiveness. The FDA reviews information that goes on a drug's professional labeling (information on how to use the drug). The FDA inspects the facilities where the drug will be manufactured as part of the approval process. FDA reviewers will approve the application or find it either "approvable" or "not approvable"

Preclinical: Computer simulations, experimental animal studies, or *in vitro* studies are performed to identify a promising drug , test for promising biologic effects and test for adverse effects. A drug company may test many related compounds to identify 1 or 2 to take further in development. The FDA is not involved in this aspect of drug development but will review the study results for any compounds that are planned for clinical (human) testing.

New Drug Application (NDA): The IND is the formal process by which a sponsor requests approval for testing of a drug in humans and includes information developed during preclinical testing regarding safety and effectiveness. There are 3 phases in clinical testing of a new drug

Phase1

Phase 1 studies are usually conducted in healthy volunteers. The emphasis in Phase 1 is on safety. The goal is to determine what the drug's most frequent side effects are often, to determine how the drug is absorbed, distributed, and excreted. The number of subjects typically ranges from 20 to 80.

Phase 2

The emphasis in Phase 2 is on effectiveness. The goal of a Phase 2 study is to obtain preliminary data on whether the drug works in people who have a specific disease or

condition. For controlled trials, patients receiving the drug are compared with similar patients receiving a placebo or a different drug. Safety continues to be evaluated and short-term side effects are studied. Typically, the number of subjects in Phase 2 studies ranges from a few dozen to about 300 after Phase 2. At the end of Phase 2, the FDA and sponsors negotiate about how the large-scale studies in Phase3 should be done. The FDA usually meets with a sponsor several times, including prior to Phase 3 studies, and pre-NDA right before a new drug application is submitted.

Phase 3

Phase 3 studies begin if evidence of effectiveness is shown in Phase 2. Phase 3 studies are usually placebo controlled and gather more information about safety and effectiveness, may test different dosages, may test the drug in different populations and usually include several hundred to about 3000 subjects.

Clinical trials: Clinical trials compare the new drug to a placebo or to an existing therapy. The standard for effectiveness may be statistical superiority to placebo or non-inferiority to an existing therapy Adverse events are recorded, because trial populations are relatively small, only the most common adverse events may be discovered also clinical trial populations are healthier than real-world populations.

The NDA is the formal request by a sponsor to market a drug in the U.S. and includes the results of preclinical and clinical studies, manufacturing information, and labeling and can be hundreds to thousands of pages. The FDA has 60 days to decide whether to review the NDA After deciding that it will review an NDA, the FDA has 10 months to make a determination (6 months for priority drugs).

Post marketing (Phase IV) Studies: As part of the approval process, the FDA may obtain commitments from the sponsor to do additional Phase 4 studies after the product is marketed. However, the FDA cannot enforce compliance. The FDA also monitors adverse events through an adverse event surveillance program.

Drug Approval Process in Europe

A sponsor has several options when seeking approval to market a new drug in Europe: a national authorization procedure, a decentralized procedure, a mutual recognition procedure,

or a centralized procedure. Products that must use the centralized procedure include the following.

1. All biologic agents or other products made using high-technology procedures
2. Products for HIV/AIDS, cancer, diabetes, neurodegenerative diseases, auto-immune and other immune dysfunctions and viral diseases.
3. Products for orphan conditions.

National authorization procedure: Each country within the EU has its own procedures for authorizing a marketing application for a new drug. A sponsor can consult the website of the regulatory agency in each country in which it is interested in obtaining marketing approval to obtain details of the approval process .A sponsor can also seek approval of several EU countries simultaneously using the decentralized or mutual recognition procedure.

Decentralized procedure: For products that fall outside the scope of the European Medicines Agency (EMA) with regard to centralized procedures, a sponsor can submit under the decentralized procedure. Using this process, a sponsor can apply for simultaneous authorization in more than one EU country for products that have not yet been authorized in any EU country. Mutual recognition procedure. With the mutual recognition procedure, a product is first authorized by one country in the EU in accordance with the national procedures of that country. Later, further marketing authorizations can be sought from other EU countries, who, rather than conducting their own review, agree to recognize the decision of the first country.

Centralized procedure: European drug approvals are overseen by the European Medicines Agency. The EMA is a decentralized body of the EU, with headquarters in London, England. It is responsible for the scientific evaluation of applications for authorization to market medicinal products in Europe (via the centralized procedure). Marketing applications for drugs for use in humans are evaluated by the Committee for Medicinal Products for Human Use (CHMP). Products that are eligible for review under the centralized procedure must meet the following criteria.

1. Biologic drugs developed by recombinant technology, controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, and hybridoma and monoclonal antibody methods medicinal products containing new active substances for the following indications: AIDS,

cancer, neurodegenerative disorders, diabetes, autoimmune diseases and other immune dysfunctions, and viral diseases

2. Orphan medicinal products other new active substances may, at the request of the applicant, be accepted for consideration under the centralized procedure when it can be shown that the product constitutes a significant therapeutic, scientific or technical innovation, or the granting of a Community authorization is in the best interests of patients at the Community level.

Pre-submission process: At least seven months prior to submitting a marketing authorization application (MAA), a sponsor must notify the EMA of their intention to submit and the month of submission. This pre-submission involves a variety of information including a document outlining the reasons the sponsor believes the application should fall under the centralized procedure. The EMA will consider the pre-submission and notify the sponsor of its decision regarding acceptance of the MAA.

Selection of rapporteur/co-rapporteur: The rapporteur is a country-specific regulatory authority within the EU. The rapporteur (reviewer) and co-rapssporteur (if needed) are identified from the CHMP members. The selection of the rapporteur is based on objective criteria, to ensure objective scientific opinion and the best use of available expertise at the EMA. The role of the rapporteur is to perform the scientific evaluation and prepare an assessment report to the CHMP. If a co-rapporteur is involved, the co-rapporteur will prepare an independent assessment report, or provide a critique of the rapporteur's report, at the discretion of the CHMP. The process for assigning the rapporteur/co-rapporteur is usually initiated at the CHMP meeting following the receipt of a letter of an intention to submit. The sponsor is notified of the rapporteur/co-rapporteur once the EMA has deemed a submission admissible.

Product naming: A sponsor's name for the drug product should be the same in all countries within the EU, except where it violates trademark rules. The sponsor should submit the proposed name in advance (usually four to six months, and not more than 12 months) of the marketing authorization application.

Drug Approval Process 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. 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. The application can be reviewed in a range of about 12-18 months. Figure 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. A comparison of drug approval process requirements in US, Europe and India is shown in Tables 1-5.

Table 1: Comparison of Drug Approval Process Requirements in US, Europe and India (Administrative Requirements)

S.NO	REQUIREMENT	US FDA	EUROPEAN	INDIA
1	Application	ND/NDA/ANDA	MAA	IND/MAA
2	Number of copies	3	1	1
3	Approval Timeline	18 months	12 months	12 months
4	Fees	No Fees	10-20 Lakh	Rs 50,000
5	Presentation	e CTD , Paper	e CTD, Paper	Paper

Table 2: Comparison of Drug Approval Process Requirements in US, Europe and India (Finished Product Control Requirements)

S.NO	REQUIREMENT	US FDA	EUROPEAN	INDIA
1	Justification	ICH Q6A	ICH Q6A	-
2	Assay	90-100%	95-105%	90-110%
3	Disintegration	Not Required	Required	Required
4	Color Identification	Not Required	Not Required	Required
5	Water Content	Required	Not Required	Required

Table 3: Comparison of Drug Approval Process Requirements in US, Europe and India (Manufacturing and Control Requirements)

S.NO	REQUIREMENT	US FDA	EUROPEAN	INDIA
1	**Number of batches**	**1**	**3**	**3**
2	Packaging	A minimum of 1,00,000 units	Not Required	Not Adressed
3	Process validation	Not required at the time of submission	Required	Required
4	Batch size	Minimum of 1,00,000 units	Minimum of 1,00,000 units	3 pilot scale

Table 4: Comparison of Drug Approval Process Requirements in US, Europe and India (Stability Requirements)

S.NO	REQUIREMENT	USFDA	EUROPEAN	INDIA
1	Number of batches	1	2	3
2	Condition	25^0/60-40^0/75 RH	25^0/60-40^0/75 RH	30^0/35-30^0/75 RH
3	Date & time of submission	3 months accelerate &3 months long term	6 months accelerate& 6 months long term	6 months accelerate&3months long term
4	Container orientation	Inverted &upright	-------	Packing which simulate the final packaging for storage &distribution
5	clause	21 CFR part 210&211	Volume 4 EU Guidelines for medicinal products	ICH QF

6	QP certification	Not required	Required	Required

Table 5: Comparison of Drug Approval Process Requirements in US, Europe and India (Bioequivalence Requirements)

S.NO	REQUIREMENT	USFDA	EUROPEAN	INDIA
1	CRO	Audited by FDA	Audited by MHRA	Audited by CDSCO
2	Reserve Sample	5 times the sample required for analysis	No such requirement	-----
3	Fasted/Fed	Must be as per OGD recommendation	No such requirement	As per CDSCO recommendation
4	Retention of samples	5 years from date of filling the application	No such requirement	3 years from the date of filling the application

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