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Comparing Drug Authorization Procedure Among India, Us, Canada and Japan

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ABSTRACT:

Drug authorization is the regulatory process by which any person /organization /sponsor gets their drugs approved for launch in the market. To submit the marketing authorization application in any country, it is important to know that country's regulatory and pharmaceutical legislation in advance. The main goals of pharmaceutical regulations include 1. Development and production for the market of new and effective therapeutics. 2. Protection of patients from unsafe/ or misbranded products. Various government agencies are involved in regulating the drugs in the market. In this study, there is involvement of regulatory requirements for drug approval namely in INDIA-CDSCO (Central Drug Standard Control Organization), US-FDA (Food and Drug Administration), CANADA-TPD (Therapeutic Products Directorate), JAPAN-MHLW (Ministry of Health, Labour and Welfare). All this agency has different procedures for drug regulation and its approval. In history, several tragic incidents happened in the drug development process due to incomplete and imperfect safety regulations. So the drug product must comply with all regulatory authorities. Once all the data have been gathered strictly and studied well, then only the drug can get marketing approval. The drug approval process of various countries is similar in some aspects but also differs in some ways. This paper also focuses on similarities and differences among the regulatory requirements and procedures of these four countries.

KEYWORDS: Drug authorization, Regulations, India, US, Canada, Japan.

INTRODUCTION

Drug approval process is the regulatory process by which any person /organization /sponsor/innovator gets their drugs approved for launch in the market. It's a very important step before introducing the drug into the market. The patient must get the drug which is having effective therapeutic value and safety.

Different tragic accidents that happened in the history of drug development due to neglect in drug evaluation or inadequate safety requirements, such as the death of ten children due to diethylene glycol contained in the elixir sulfanilamide in 1938 in US.[1,2]

Based on marketing interest, the pharmaceutical market can be divided into two groups: Regulated and emerging markets. The regulated market involves those countries where there are defined regulatory requirements set by the regulatory bodies of that country. The emerging market countries still lag behind in putting forward properly defined regulations for drugs. United States (US) and the EU are the biggest regulated markets, *-whereas ROW (Rest of the World) market includes all the emerging markets like Brazil (LATAM), Tanzania (Africa), Russia (CIS) etc. The fact that all regulators worldwide share the same aims, but still they do not adopt a consistent approach to drug approval process, and as a result, medicines are often approved quicker in some countries than others. So, there is need for a harmonized drug regulation globally.[3,4]

1.1 Drug Regulations and Laws "Regulations" are the rules established by an agency that interprets the laws to facilitate their practical implementation. These regulations are designed to ensure safety, efficacy, and quality of the drugs. This is done by including premarket screening and evaluation of new pharmaceuticals, inspection of

manufacturing facilities, and postmarketing surveillance of drugs till the approval.

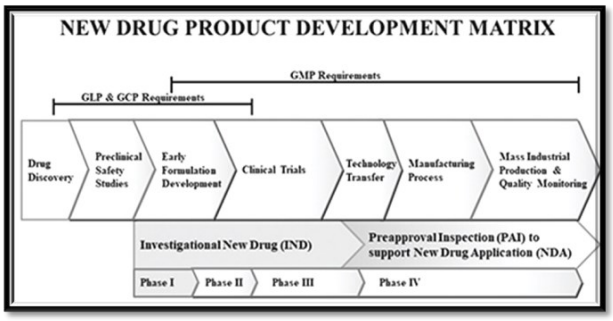

Figure: 1.Regulation of new drug

The product development should comply with most regulatory authorities. The list of regulatory bodies as per the country are given below:

COUNTRIES	REGULATORY AGENCIES
USA	USFDA
European Union	EMEA
Japan	MHLW
India	CDSCO
UK	MHRA
Australia	TGA
Canada	Health Canada
South Africa	MCC
Brazil	ANVISA
China	SFDA
Switzerland	SWISSMEDIC
Korea	KFDA
Sri Lanka	MOH

Table: 1.Regulatory bodies as per the country

1.2 What is drug approval/authorization process?

The drug approval process is in place to ensure that only drugs that are effective and are safe are approved. A full marketing authorization is the standard type, which requires a comprehensive amount of information on clinical benefit and safety for the drug to be approved. Once all the required data have been gathered, then the drug can receive full marketing authorization.

There are step by step stages to be followed for the drug approval which includes:

1. Pre-clinical phase: This is a first step. Before a drug company can test an experimental treatment on humans, it must prove that drug is safe and effective in animals.

2. Phase 1 clinical trials: In this round of clinical trials, the drug company require to establish the safety of drugs in humans. Drug researchers administer the treatment to healthy individuals just to check the toxicity at higher doses.

3. Phase 2 clinical trials: In the second round of clinical trials, researchers give the treatment to patients who have the disease to assess the drug's efficacy.

4. Phase 3 clinical trials: In this researchers work with the FDA to design a larger trial to test the drug's ideal dosage, patient population and other factors that could decide whether the drug is approved as per report. This could include thousands of participants.

5. New drug application: After the company collects, analysis of all data from the clinical trials; it files a new drug application to the FDA. The application includes clinical trial data, preclinical information and details on the drug's manufacturing process. As there is contrast in regulatory process of every country so the stages of approval of drug may vary. [5]

2.LITERATURE REVIEW

1) **"Regulatory Requirements for Registration of API in US and EU".**
   There are different regulatory bodies country wise. For API registration in US, the main body is FDA which approves the products. It also has different agencies performing different tasks. EMEA is important regulatory body in Japan whose main work is to scientific evaluation of the authorization of medicinal products. DMF is also filed which is very important document and its contents also differs in countries. [3]
2) **"Drug Approval Process: A Contrastive Approach".**
   In this paper, there is brief on regulatory bodies. Each of these has several objectives to be performed. It also includes contrasting the drug approval between Europe, US and India. The approval of drug is required to effective and safe delivery of drug to all living beings. All these countries are highly regulated and have different phases of drug approval. [1]
3) **"A comprehensive study on regulatory requirements for development and filing of generic drugs globally".**
   This article has overview on filling requirements of generic in countries like USA, Europe, Brazil, Africa, Russia, Hong Kong. The regulatory agencies should be harmonized well to cope with all different guidelines. [4]
4) **"Regulatory Aspects regarding Drug Filling Process in India, US & Europe".**
   The basic criteria for filling NDA includes different points. In India the regulatory bodies work efficiently to provide safe drugs. This is done by following all requirements for drug approval and submission of documents. CTD (Common Technical Document) is also important and submitted for drug approval. Then the principal differences are mentioned country wise & their regulations. [6]
5) **"Regulatory Requirements & Drug Approval Process in India, Europe and US".**

In this, regulatory strategies of US, Europe and India has described. In India the main bodies for drug control includes CDSCO, DCGI. EMEA is main body in Europe and FDA in US. Certain similarities and dissimilarities are there among these countries for drug approval. [15]

6) **"New Drug Approval Procedure in Different Countries: A Review".**
The main focus of this paper is based on the processes for drug approval in different countries like India, USA, Australia, China, Canada and European countries. There is also similarity among the countries and somewhat they also differ. All the information to be submitted regarding drugs is similar for all agencies, but the time, fees, and review process differs. [17]
7) **"Comparison of the drug approval processes in the US, the EU and Canada".**
It majorly focuses on the processes of marketing authorization for 3 different countries. The US and EU both are the members of European Union and are very similar in regulations of drug marketing. The Canadian system of drug marketing has some differences. The difference in terms of review process timing, clinical trials information, fee etc. [11]
8) **"Regulatory Strategies for Filing of NDA in ICH Countries (Us, Europe and Japan)".**
In this paper, there is a discussion on the regulatory framework of ICH countries. All the 3 countries are well developed and are similar in aspects of drug approval. The main mission of ICH is uniform interpretation and application of technical guidelines and requirements. By this, the duplication of work is reduced and there is uniformity in drug research and development. [13]
9) **"The Drug Approval Process in the U.S., Europe, and Japan".**
The mission of all these countries is to harmonize and regulate the drug approval process. There are details on the stepwise procedure of drug registration for all these countries. The format of filling out an NDA is similar in all the 3 countries. Their efforts for proper harmonization and regulation should be always increased. [18]
10) **"Flexible and Expedited Regulatory Review Processes for Innovative Medicines and Regenerative Medical Products in the US, the EU, and Japan".**
In this article, there is a flexible and expedited review procedure for new drugs, and cell and gene therapies in the US, the EU, and Japan are explained. All the drugs and regenerative medical products granted for conditional approval are analyzed. Each of these countries has a proper elaborated framework of regulatory body to work efficiently. [19]

3. DRUG AUTHORIZATION IN INDIA

The D&C Act 1940 and Rules 1945 were passed by the Parliament of India to regulate the manufacture, distribution and sale of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO), and the Drugs Controller General (India) [DCGI] were established. After then in 1988, the Indian government added Schedule Y to the D&C Rules 1945. Schedule Y describes the guidelines and requirements for clinical trials, which were again revised in 2005. An application to conduct clinical trials in India should be submitted along with the data of chemistry, manufacturing, control and animal studies to DCGI. To determine the maximum tolerated dose in humans, adverse reactions, etc. on humans, Phase I clinical trials are conducted. The therapeutic uses and effective dose ranges are determined in Phase II trials. 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. After the NDA approval, when a company is allowed to distribute and market the product, it is considered to be in Phase IV trials. Similarly, the format used for the presentation of the dossier submitted for approval of drug is also different. In 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.[6]

In India NDA is filed for permission to grant and approval of new drugs. It contains all the clinical and preclinical data and information regarding manufacturing processes. To obtain permission the sponsor has to fill in all information to NDA and then the analysis of the drug starts. After NDA receives it, the technical screening process starts and ensures all the required data has been submitted. After the review period, the sponsor may get these 3 actions:

1. Not approvable
2. Approvable
3. Approval.

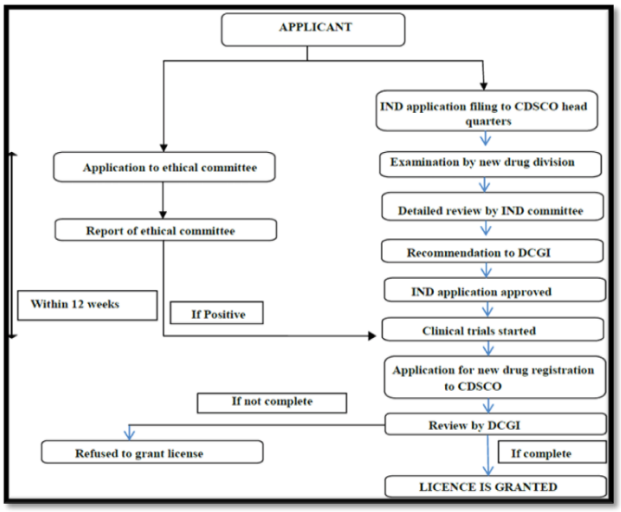

Figure 2. New drug registration process in India

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

3.1 Stages of approval

1. Submitting the Clinical Trial application to study safety and efficacy.

2. Requirements for permission of new drugs approval.

3. Changes of post-approval in biological products: quality, safety and efficacy documents

4. Collecting and documenting of the quality information for drug submission for NDA.

After the NDA approval, when a company is allowed to distribute and market the drug, it is considered to be in Phase IV trials, in which new populations, long-term effects, etc. are explored. [7]

4. DRUG AUTHORIZATION IN U.S.

The USA is the major market for the pharmaceutical industry. This country has evolved from no regulations in the 18th century to one of the most highly regulated and admired regulatory authorities in the world known. The Food and drug administration (FDA) within the U.S. Department regulates the drug approval system in the United States with the help of six product centers involving: the Center for Drug Evaluation and Research (CDER). Drug registration in the USA is mainly divided into two types of applications: 1. New Drug Application (NDA) & 2. Abbreviated New Drug Application (ANDA). ANDA is filed for generic drugs that require market authorization. NDA is the application submitted by the sponsor for drug approval to FDA. It must contain data regarding chemistry, pharmacology, medical biopharmaceutics, and statistics. It will also include the data gathered during animal and human clinical trials.[8]

FDA approval of a drug means that data on the drug's effects have been thoroughly reviewed by CDER, and the drug is determined to provide benefits that are known and potential risks for the population. The FDA usually responds to the pharmaceutical company within 12 months of submission, although there are exceptions to this norm. The drug approval process takes place in the given below format:

• Analysis of the target condition and available treatments—FDA reviewers analyze the condition or illness for which the drug is intended and evaluate the current treatment, which provides the context for the drug's risks and benefits.

• Assessment of benefits and risks from clinical data—The FDA team reviewers evaluate and review clinical benefit and risk data submitted by the sponsor, taking into account any uncertainties that may occur due to imperfect or incomplete data. Generally, the agency expects that the sponsor will submit results from two well-designed clinical trials, to be sure that the findings from the first trial are not the result of chance or bias.

Strategies for managing risks—All drugs contain risks. The risk management strategies include an FDA-approved drug label, which clearly describes the drug's benefits and side effects, and how the side effects can be managed.

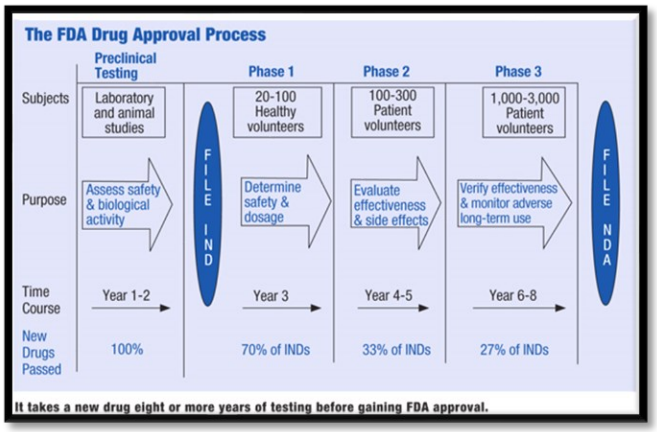

Figure: 3. Drug approval process in the US

4.1 FDA approval process

It begins only after the submission of an investigational new drug (IND). The IND application should provide high-quality preclinical data to provide proper justification of clinical data on humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed. The next step includes phase I, phase II and phase III clinical trials. A new drug application (NDA) can be filed only when the drug has successfully passed all phases of clinical trials and includes all animal and human data, the pharmacokinetics of the drug and its manufacturing labelling.[8,9,19]

4.2 ANDA (Abbreviated New Drug Application)

An abbreviated new drug application (ANDA) contains all data that is sent to the FDA for further review and approval of a generic drug product. Generic drug applications are termed "abbreviated" because they are generally not required to include preclinical (animal) and clinical (human) data for safety purposes. Instead, generic applicants must scientifically prove that their drug performs in the same manner as the innovator drug. Another way to applicants prooving that a generic product performs in the same way as the innovator drug is to measure the time it takes the generic drug to reach the bloodstream in healthy volunteers. [10, 20]

5. DRUG AUTHORIZATION IN CANADA

The regulation system of regulating drug products is very similar to regulations in the United States. Health Canada regulates pharmaceutical drugs (prescription and non-prescription) and medical devices for human use. All drug products sold in Canada must be approved by the Therapeutic Products Directorate (TPD). The pharmaceutical market in Canada is the eighth largest in the world. For the new drug submission, the drug must undergo all the safety and efficacy procedures. When an NDS is submitted to TPD, it first undergoes an administrative screening process to ensure that all necessary parts are involved and in the required format. After this, the file is sent to the appropriate bureau for reviewing the drugs in a given therapeutic area. If a sponsor is able to provide all required data and fulfils all regulatory requirements, Health Canada will grant a Notice of Compliance (NOC) and assign a drug identification number (DIN). DIN is a unique number given to every drug. Once a drug has received a NOC and DIN, the sponsor is authorized to sell their product on the market. But if, the sponsor is unable to provide sufficient data of safety and efficacy, Health Canada may issue a Notice of Noncompliance and request that the sponsor submit additional required evidence.

5.1 Important Terms Used are

Notice of Deficiency (NOD): the review cannot further proceeds because of deficiencies in the file.

Notice of Deficiency: Withdrawal (NOD/w): if the response to an NOD is improper, the TPD will issue a NOD/w letter, indicates the company must withdraw the application.

Notice of Non-compliance (NON): indicates the review is complete and the file submitted is deficient or incomplete. It is usually not as severe as an NOD.

Notice of Non-compliance: Withdrawal (NON/w): if the response to a NON is inadequate, the company must withdraw the submission.

Notice of Compliance (NOC): once all issues have been resolved, the TPD will issue an NOC.

Priority Review: A review status granting eligible new drug submissions and supplements to new drug submissions at short time review. This status is granted following review and approval of a request submitted by the sponsor of the drug.

5.2 Other factors in Canadian Approval process

There are many other factors to be remembered at the time of review of drug. One is that under the Canadian Health Act, medically necessary prescription drugs are provided without charge to inpatients or outpatients when administered in a hospital. Health Canada agreed that it would oversee all manufacturing and formulation information. Also agreed to issue declarations of bioequivalence between generic and reference products to help smoothening the drug approval process. The Government of Canada also has external advisory committees for the review process. The role of external advisory committees is mainly focused on cost-effectiveness benefits rather than drug therapeutic effectiveness.[11,12]

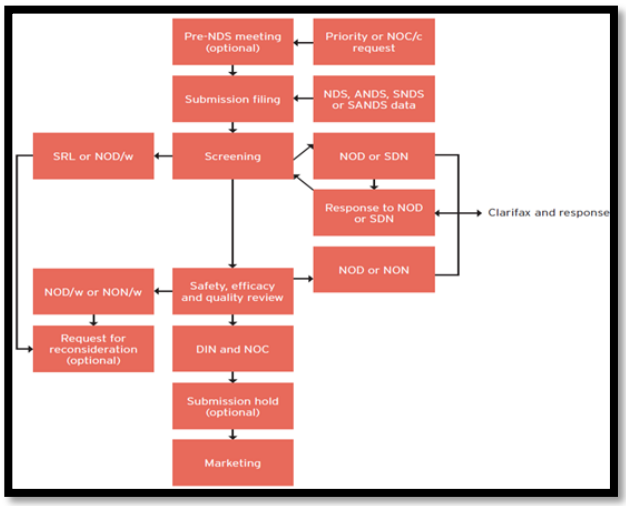

Figure 4 Overview of drug approval procedure in Canada

6. DRUG AUTHORIZATION IN JAPAN

In Japan the main regulatory bodies include PMDA (Pharmaceuticals and Medical Device Agency) and MHLW (Ministry of Health, Labour and Welfare).The application submitted for approval of drugs is reviewed as per submitted documents by MHLW officers and the Central Pharmaceutical Affairs Council (CPAC). Application submitted must include the required data of clinical trials, chemistry, pharmacology and manufacturing process. All the decisions are taken by the MHLW Drug Organization and National Institute of Health Sciences (NIHS) for intensifying the review and approval system of drugs and medical devices. Then the evaluation center of the NIHS is responsible for reviews after the submission of NDA to the reviews by the subcommittee of the CPAC. It takes time for NDA review and then response is made. If there is no approval of drug, then no grant of manufacturing process and import license in Japan. Hence application for approval and license is made simultaneously in Japan. The application filed for approving drug must contains all the relevant information (manufacturing site, clinical trials). Then after review process starts and after completion of it final decision is made. The review time usually is 18 months. Two types of review in Japan includes priority and standard review. [13, 18]

6.1 Requirements for IND approval

1. Documents that give the reason why the request for the clinical study was made

2. Clinical study protocol
3. Explanatory materials and consent form
4. Sample of the case report form (CRF) (The sample is not required if information to be contained in the CRF is explicitly stated in the protocol.)

Investigator's Brochure is also very important.

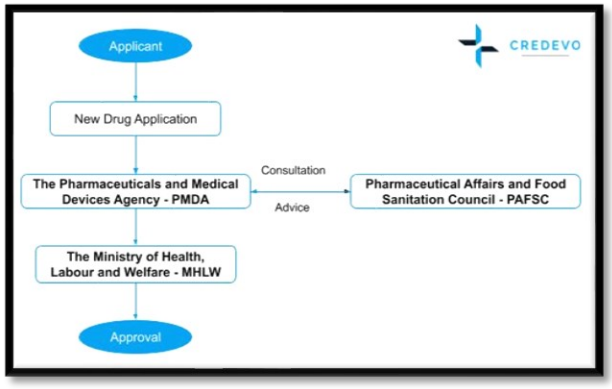

Figure 5 Process flow of drug approval

Japan's regulatory system demands the IND Application documents be prepared in the Common Technical Document (CTD) format. CTD format is less time-consuming and very convenient. Before sending an application for Investigational New Drug (IND) to the PMDA, the applicant may schedule a meeting (consultation with the PMDA), which ensures smooth and easy processing of IND approval. Subsequent to the application submission, PMDA evaluates the pre-clinical and clinical data. It may probably take 30 days for the initial IND and then 14 days for the second and other consecutive INDs.

6.2 Review Process

The queries received from PMDA should be answered by the applicant properly. After PMDA completes its review, the IND application will be transferred to Institutional Review Board (IRB) for the review. Once IRB provides a required response, IND application will be approved after which, the clinical trials will be initiated on humans. [14, 15, 17]

Table: 2.Compare and Contrast the regulatory difference between drug approval in India, US, Canada, Japan

SR.NO.	PARAMETERS	INDIA	U.S.	CANADA	JAPAN
1.	Agency	CDSCO	USFDA	Health Canada of HPFB	PMDA MHLW
2.	Application	IND/NDA	ANDA / NDA	ANDS/NDA	ANDA/NDA
3.	Scope	Drug Development Tools: •Biomarkers •Animal Models	Drug Development Tools for which there are formal Qualification programs: • Biomarkers •Clinical Outcome Assessments (patient reported outcomes, clinician -reported outcomes, observer reported outcomes and Performance Outcomes (PerfO)) •Animal Models for use under the FDA Animal Rule	Drug Development Tools: •Biomarkers•Clinical Outcome Assessment	Drug Development Tools: •Biomarkers & Companion Diagnostics •Animal Models
4.	Data Requirement	Biological activity, Clinical studies, Preclinical, and Immunogenicity studies	Analytic data that show similar to the reference, animal studies, Clinical studies, identity of mechanism of action	Clinical trials data, Animal studies, Chemistry and Pharmacology of drug	Clinical studies, Preclinical, and Immunogenicity studies
5.	Fees	None	None	Yes, Fees to be paid.	None
6.	Stability requirement	Long Term and Accelerated	Long Term and Accelerated	Long Term and Accelerated	Not necessary
7.	Approval timeline	~18 Months	12-18 moths	6months-2yrs	~18 Months
8.	Presentation	eCTD & Paper	CTD & Paper	eCTD	eCTD & Paper

CONCLUSION:

Normally, the drug approval process comprised mainly two steps; first is submitting application to conduct clinical trial and second is applying to competent regulatory authority for marketing authorization of the drug. The new drug approval process of some countries is similar in some of the aspects whereas it also differs in some other respects. In all countries, data submitted to regulatory authorities regarding the quality, safety and efficacy of drugs is similar, whereas, the time, fee and review process of clinical trials

and marketing authorization differs. There are laws that require to be followed for drugs to be developed, tested, trailed, and manufactured in accordance to the guidelines so that they are safe, efficient and the patient's well-being is protected. Regulated countries like US, Japan and Canada have understood the importance of qualification of drug development tools. In semi-regulated markets like India, still there is a lot to be done.

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