International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 2364-2370 www.ijprajournal.com ISSN: 2249-7781

New Drug Approval Process in India Emphasis on Clinical Trials

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Submitted: 20-02-2023 Accepted: 28-02-2023

ABSTRACT:

A regulatory process, by which a person/organization/sponsor/innovator gets authorization to launch a drug in the market, is known as drug approval process. In general, a drug approval process comprises of various stages: application to conduct clinical trials, conducting 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. This work focuses on the drug approval process in India.

Key words: Drug approval process,Clinical trials,Marketing

I. INTRODUCTION:

Approval of new drug in india:

When a company in India wants to manufacture/ import a new drug it has to apply to seek authorization from the licensing authority(DCGI) by filing in Form 44 also give in the data as given in Schedule Y of drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its effectiveness and safety in Indian population it has to conduct clinical trials in agreement with the guidelines specified in Schedule Y and submit the report of analogous clinical trials in specified format.

But a figure is there in Rule- 122A of drug and Cosmetics Act 1940 and Rules 1945 that the licensing authority may waive certain trails if he considers that in the interest of public hygiene he may grant authorization for import of new drugs grounding on the data of the trials done in other countries. also there's another outline in Rule-122A which says that the clinical trials may be waived in the case of new drugs which are accept and being used for some times in other countries

Reverse Image Search

Section2.4(a) of Schedule Y of drugs and Cosmetics Act 1940 and Rules 1945 says for those medicine substances which are discovered in India all phases of clinical trials are required.

Section2.4(b) of Schedule Y of drugs and Cosmetics Act 1940 and Rules 1945 says that for those medicine substances which are find in countries other than India; the aspirant should give in the data available from other countries and the licensing authority may bear him to reprise all the studies or permit him to do from Phase III clinical trials.

Section2.8 of Schedule Y of drugs and Cosmetics Act 1940 and Rules 1945 says that the licensing authority may bear pharmacokinetic studies(Bioequivalence studies) first to show that the data generated in Indian population is the same to data generated abroad and also bear him to do with Phase III trials

The process of approval of new drug in India is a extremely complex process, which should meet obligatory requirements along with NDA to FDA. The need of the present work is to study and document the requirements for the process of approval of new drug in India with emphasis on clinical trials as per Drugs Control department, Government of India

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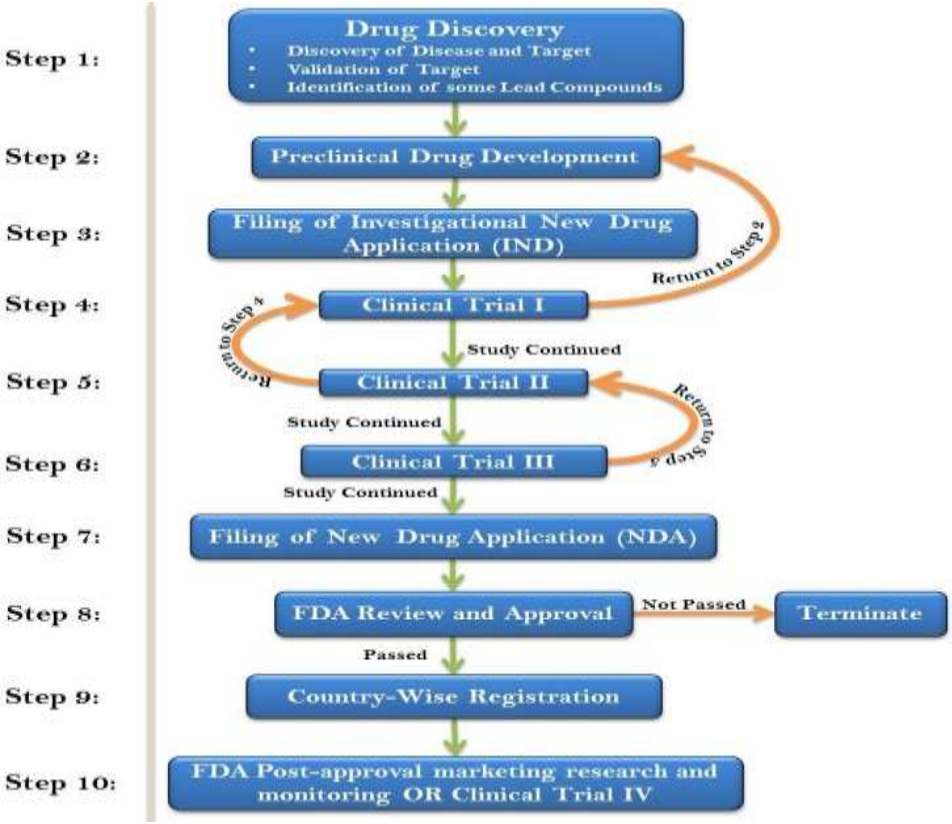

Fig 1: Steps of drug approval process in india

II. DISSCUSSION:

Safety and efficacy of the drug product for use in humans is essential before the drug product can be approved for import or manufacturing of new drug by the applicant by Central medicines Standard Control Organization(CDSCO). The regulations under drugs and Cosmetics Act 1940 and its rules 1945, 122A, 122B and D and further appendix I, IA and VI of Schedule Y, describe the information demand for blessing of an operation to import or manufacture of new drug for - 8 Through the International Conference on Harmonization ICH) process, the Common Technical Document(CTD) guidance has been developed for Japan, European Union, and United States

Drug discovery:

Drug discovery is the process through which implicit new therapeutic entities are identified, using a combination of computational, experimental, translational, and clinical models Involves-Discovery of diseses and target ,Validation of target, Identification of some lead compounds

Pre-clinical drug development:

The preclinical phase of drug development refers to testing of activity and exertion and toxin of a drug candidate in in vitro and in vivo studies before testing in patients can be performed.

A lead candidate is identified, a typical preclinical development program consists of six major efforts: manufacture of drug substance (DS)/active pharmaceutical ingredient (API); preformulation and formulation (dosage design); analytical and bioanalytical methods development and validation; metabolism

Investigational new drug application (IND):

An Investigational New Drug Application (IND) is a appeal from a clinical study sponsor to obtain authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological result to

Phases Of Clinical Trials:

- **Pre Clinical Study**: Mice, Rat, Rabbit, Monkeys
- **Phase I**:Human Pharmacology Trial – estimation of safety and tolerability

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- **Phase ll**:Exploratory trial- estimation of effectiveness and short term side effects
- **Phase lll**:Confirmatory trial - confirmation of therapeutic benefits
- **Phase IV:**Post marketing trial-studies done after drug approval

○ **Drug Cantroller General of india (DCGI):**

Clinical exploration is coordinated in India by Drug Controller General of India(DCGI). The office of DCGI runs under CDSCO. It has main responsibility of regulating clinical trials in India. Event related to product blessing and morals, clinical trials, prolusion of new drug , and import licenses of new drug are hold by DCGI

○ **Drugs Technical Advisary Board (DTAB):**

It has particularize experts and this instruction the central and state governments on all specialized matters arising out of the enforcement of drug control. No rules can be made by the central government without consulting DTAB board.

○ **Drugs Consultative Committee:**

It has central and state drug control officers as members. Its main function is to assure the drug control measures and apply them relatively over all the countries.

○ **Genetic Engineering Approval Committee (GERC):**

It is authority to approve r-DNA medicinal products. GEAC's part is to estimate the bio-safety /environmental safety aspect of the biotechnological product.

New Drug application :

NDA is an operation submitted to the FDA for authrization to request a new drug. To gain this authrization a gurantor submits preclinical and clinical test data to NDA for analyzing the drug details , description of manufacturing procedures. After NDA received by the agency, it undergoes a technical webbing . This assesment ensure that satisfactory data and information have been submitted in each region to justify "form" the operation that is FDA formal review

FDA Review and approval:

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

1. Not approvable- in this letter list of defect and explain the purpose.
2. Approvable - it means that the drug can be approved but minor defect that can be put right like-labeling changes and possible request dedication to do post-approval studies.
3. Approval- it state that the drug is approved. If the action taken is either an approvable or a not approvable, then FDA provides applicant with an occasion to connect with agency and discuss the deficiencies

Some of the rules and guidelines that should be followed for regulation of drugs in India are:

- Drugs and Cosmetics Act 1940 and its rules 1945
- Narcotic Drugs and Psychotropic Substances-1985
- Drugs Price Cantrol Order-1995
- Consumer Protection Act-1986
- Factories Act-1948
- ICH GCP Guidelines
- Shedule Y Guidelines
- ICMR Guidelines
- Registry of trial

Various Regulatory Agencies that are involved in drug regulation in india:

- DCGI: www.cdsco.nic.in
- CDL: www.mohfw.nic.in/kk/95/ia/95ia0701.htm
- RCMC (Review Committee on Genetic manipulation)www.dbtindia.nic.in
- ICMR:www.icmr.nic.in
- Central Excise
- State food and drug administration

Stages of approval:

1. Presentation of Clinical Trial operation for assessing safety and effectiveness.
2. Condition for authorization of new drugs approval.
3. Post approval changes in biological products: quality, safety and efficacity documents.
4. Composition of the quality informatio n for drug presentation for new drug approval

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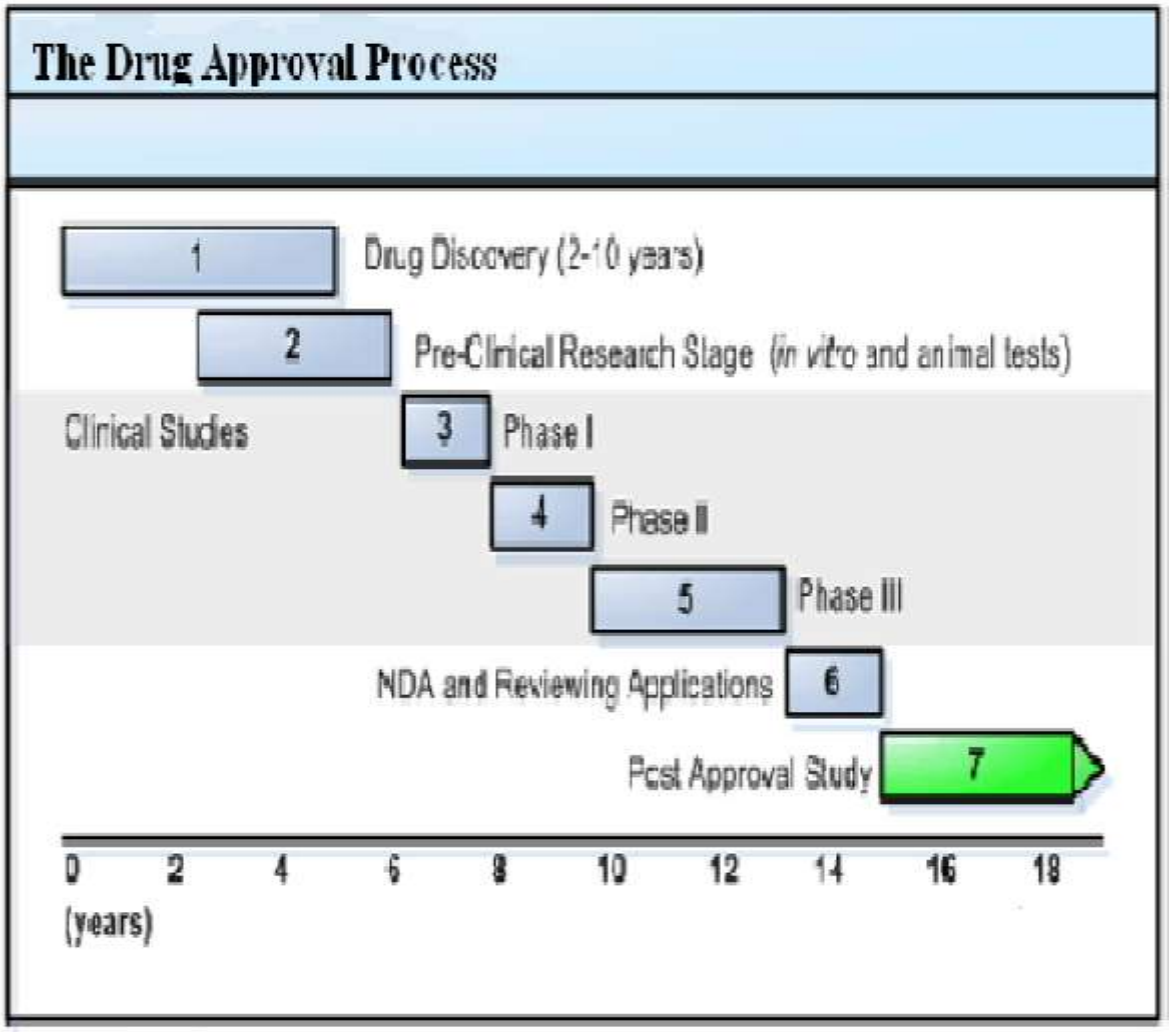

Fig 2: The drug approval process as a function of time

1. Presentation of clinical trial application for evaluating Safety and Efficacy

All the data listed below has to be produced

a) Phase-I and Phase-II clinical trial

- General Information
  - Prolusion about company: brief description about company
  - Administrative headquarters
  - Manufacturing installation
  - Regulatory and intellectual property status in other countries
  - Patent information status in india and other countries
- Chemistry manufacturing control
  - Product description
  - Product development
  - Strain details
  - Information on drug substance
  - Information on drug product
- Non clinical data references: schedule Y, correction interpretation 2005, drugs and cosmetics rule 1945
- Proposed phase-I/II studies:protocol for phase-I/II studies

b) Phase-III clinical trial

Same as phase I & phase II clinical trial

- General information
- Chemistry manufacturing control
- Non –clinical data
- Proposed phaseIII studies

2. conditions for authorization of New drugs Approval

The manufacturer / gurantor have to submit operation on Form 44 for authorization of New drug Approval under the vittles of drug and

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Cosmetic Act 1940 and Rules 1945. The document design is as per the International submission conditions of Common Technical Document (CTD) and has five Modules.

Module I: Administrative/Legal Information

This module should carry documents specific to each around; for illustation, operation forms or the proposed marker for use in the around. The content and format of this module can be define by the relevant regulatory cantrol

Module II: Summaries

Module 2 should begin with a general prolusion to the medicinal, including its pharmacologic class, mode of action and proposed clinical use. In general, the prolusion should not exceed one runner. The preface should include proprietary name, nonproprietary name or common name of the drug substance, company name, capsul form, strength, route of administration, and proposed suggestion(s). It contains the CTD summaries for quality, safety, effectiveness information. This module is veritably important, as it provides detailed summaries of the various sections of the CTD. These include: A veritably short preface. Quality overall summary, Non clinical overview, Clinical over view, Non clinical written and tabulated summaries for pharmacology, pharmacokinetics & toxicology.

Module III: Quality information (Chemical, pharmaceutical and biological)

Information on quality should be presented in the structured format described in the guidance M 4Q. This document is intended to provide guidance on the format of a registration operation for drug substances and their corresponding medicine products. It contains of all of the quality documents for the chemistry, manufacture, and controls of the drug substance and the drug product.

Module IV: Non-clinical information

Details of safety should be presented in the structured format described in the guidance M 4S. The purpose of this section is to present a critical analysis of the non-clinical data pertinent to the safety of the medicinal product in the intended population. The analysis should consider all applicable data, whether positive or negative, and should explain why and how the data support the proposed suggestion and defining information. It gives final dupe of all of the final nonclinical study reports

Module V: Clinical information

Details of effectiveness should be presented in the structured arrangement described in the guidance M 4E. It gives clinical summary including biopharmaceutics, pharmacokinetics and pharmacodynamics, clinical pharmacology studies, clinical effectiveness, clinical safety, synopses of the individual studies and final dupe of detailed clinical study reports

3.Prepration of the quality information for drug submission for new drug approval

1) Drug substance (name,manufacturer)
2) Characterization (name,manufacturer)
- Physicochemical characterization
- Biological characterization

3) Drug product (name,dosage form)
4) Control of drug product (name,dosage form)
5) Appendies
- Facilities and equipment (name,manufacturer)
- Safety evalution adventitious agents (name,dosage form,manufacturer)

For the import or manufacture of new drug for clinical trials, there are several steps that have to be followed

Application for permission to import New Drug

1) a. No new Drug shall be imported, except under, and in agreement with, the authorization granted by the Licensing Authority as defined in clause(b) of rule 21

b. An operation for entitlement of authorization to import a new medicine shall be made in Form 44 to the Licensing Authority, accompanied by a figure of fifty thousand rupees

handed further that where a posterior operation by the same aspirant for that medicine, whether in modified lozenge form or with new claims, is made, the figure to accompany similar operation shall be fifteen thousand rupees;

provided handed further that any operation entered after one time of the entitlement of blessing for the import and trade of new medicine, shall be accompanied by a figure of fifteen thousand rupees and similar information and data as needed by excursus 1 or excursus 1A of Schedule Y as the case may be

2) The importer of a new medicine when applying for authorization undersub-rule(shall submit data as given in excursus 1 to Schedule Y including the results of original clinical trials carried out in

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agreement with the guidelines specified in that Schedule and submit the report of similar clinical trials in the format given in excursus II to the said Schedule provided that the demand of submitting the results of original clinical trials may not be necessary if the medicine is of such a nature that the licensing authority may, in public interest decide to grant similar authorization on the base of data available from other countries

Provided further that the submission of conditions relating to Beast toxicology, reduplication studies, teratogenic studies, perinatal studies, mutagenicity and Carcinogenicity may be modified or relaxed in case of new medicines approved and retailed for several times in other countries if he's satisfied that there's acceptable published substantiation regarding the safety of the medicine, subject to the other vittles of these rules.

3) The Licensing Authority, after being satisfied that the medicine if permitted to be imported as raw material(bulk medicine substance) or as finished expression shall be effective and safe for use in the country, may issue an import authorization in Form 45 and/ or Form 45 A, subject to the conditions stated therein

4) Handed that the Licensing Authority shall, where the data handed or generated on the medicine is shy, intimate the aspirant in jotting, and the conditions, which shall be satisfied before authorization, could be considered

Permission to import or manufacture fixed dose combination (122-D):

1) An operation for authorization to import or manufacture fixed cure combination of two or further medicines as defined in clause(c) of rule 122 E shall be made to the Licensing Authority as defined in clause b) of rule 21 in Form 44, accompanied by a figure of fifteen thousand rupees and shall be accompanied by similar information and data as is needed in excursus VI of ScheduleY.

2) The Licensing Authority after being satisfied that the fixed cure combination, if approved to be imported or manufactured as finished expression shall be effective and safe for use in the country, shall issue authorization in Form 45 or Form 46, as the case may be, subject to the conditions stated therein;

Provided that the Licensing Authority shall where the data handed or generated on the fixed cure combination is shy, intimate the aspirant in jotting, and the conditions which shall be satisfied before entitlement of blessing/ authorization could be considered

Application for authorization to conduct clinical trials for new drug (122-D):

1) No clinical trial for a new medicine, whether for clinical disquisition or any clinical trial by any Institution, shall be conducted except under, and in agreement with, the authorization, in jotting, of the Licensing Authority defined in clause (b) of rule 21

2) An application for entitlement of permission to conduct

- Human clinical trials (Phase-I) on a new medicine shall be made to the Licensing Authorit in Form 44 accompanied by a fee of fifty thousand rupees and such information and data as required under schedule Y
- Exploratory clinical trials (Phase-II) on a new drug shall be made on the base of data emerging fromPhase-I trial, accompanied by a figure of twenty-five thousand rupees
- Confirmatory clinical trials (Phase-III) on a new drug shall be made on the basis of data emerging from Phase-II and where necessary ,data emerging from Phase-I also,and shall be accompanied by a figure of twenty-five thousand rupees

Provided that no separate figure shall be required to be paid along with operation for import/manufacture of a new medicine based on successful completion of phases of clinical trials by the aspirant.

Provided further that no figure shall be required to be paid along with the operation by Central Government or State Government institutes involved in clinical exploration for conducting trials for academic or exploration purposes.

3) The Licensing Authority after being satisfied with the clinical trials,shall grant authorization in Form 45 or Form 45A or Form 46 or Form 46-A, as the case may be, subject to the conditions stated therein:

Provided that the Licensing Authority shall, where the data provided on the clinical trials is inadequate, intimate the aspirant in jotting, within six months, from the date of similar suggestion or such extended period, not exceeding a further period of six months, as the Licensing Authority may, for reasons to be recorded, in jotting, permit, intimating the conditions which shall be satisfied before authorization could be considered:

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Suspension or cancellation of Permission / Approval (122-DB):

If the importer or manufacturer below this Part stall to comply with any of the conditions of the permission or approval, the Licensing Authority may, after giving an opportunity to show because why such an order should not be passed, by an order in writing stating the cause there for, suspend or drop it.

Appeal (122-DC):

Any human aggrieved by an order passed by the Licensing Authority lower than this Part, may within sixty days from the date of such order, appeal to the Central Government, and the Central Government may after such enquiry into the matter as is considered required, may pass such order in relation thereto as it thinks fit.

III. CONCLUSION:

From the above review it can be concluded that, all clinical studies reports and related information regarding the approval of new drug in India should provide the necessary conditions along with the NDA to FDA

Generally, the drug approval process comprised mainly the two way, operation to conduct clinical trial and application to the regulatory authority for marketing authorization of drug

The clinical studies reports and related information for process of approval of new drug in India with emphasis on clinical trials should follow the Schedule Y, the Drug and cosmetics Rules 1945 rules given by the CDSCO. The rules that should be followed are enlisted in rule numbers 122A, 122B, 122D and 122DA.

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