Review Article

PROCESS OF APPROVAL OF NEW DRUG IN INDIA WITH EMPHASIS ON CLINICAL TRIALS

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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.

Keywords: Drug approval process, Clinical trials, Marketing.

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 permission from the licensing authority (DCGI) by filing in Form 44 also submitting the data as given in Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945. In order to prove its efficacy and safety in Indian population it has to conduct clinical trials in accordance with the guidelines specified in Schedule Y and submit the report of such clinical trials in specified format.

But a provision is there in Rule- 122A of Drugs and Cosmetics Act 1940 and Rules 1945 that the licensing authority may waive certain trails if he considers that in the interest of public health he may grant permission for import of new drugs basing on the data of the trials done in other countries. Similarly there is another provision in Rule- 122A which says that the clinical trials may be waived in the case of new drugs which are approved and being used for several years in other countries.

Section 2.4 (a) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says for those drug substances which are discovered in India all phases of clinical trials are required.

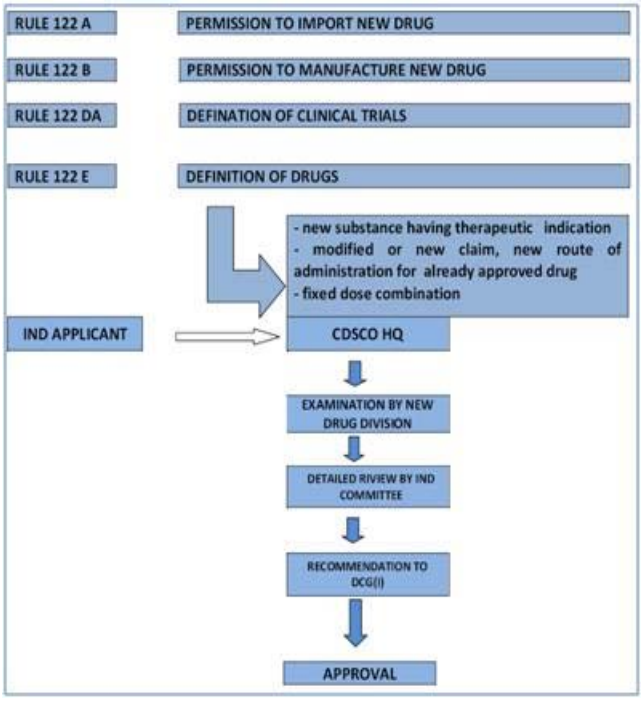
Section 2.4 (b) of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that for those drug substances which are discovered in countries other than India; the applicant should submit the data available from other countries and the licensing authority may require him to repeat all the studies or permit him to proceed from Phase III clinical trials.

Section 2.8 of Schedule Y of Drugs and Cosmetics Act 1940 and Rules 1945 says that the licensing authority may require pharmacokinetic studies (Bioequivalence studies) first to show that the data generated in Indian population is equal to data generated abroad and then require him to proceed with Phase III trials.

In summary, the exact requirements of Clinical trials may change from case to case and depend on the extent to which licensing authority is satisfied about its safety and efficacy.[1-6]

The process of approval of new drug in India is a very complicated process, which should meet necessary 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.

Figure 1: Pictorial representation drug approval process in India



DISCUSSION

Demonstration of 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 Drugs Standard Control Organization (CDSCO). The regulations under Drugs and Cosmetics Act 1940 and its rules 1945, 122A, 122B and 122D and further Appendix I, IA and VI of Schedule Y, describe the information required for approval of an application to import or manufacture of new drug for marketing.[6-8]

Through the International Conference on Harmonization (ICH) process, the Common Technical Document (CTD) guidance has been developed for Japan, European Union, and United States.

Most countries have adopted the CTD format. Hence, CDSCO has also decided to adopt CTD format for technical requirements for registration of pharmaceutical products for human use.

It is apparent that this structured application with comprehensive and rational contents will help the CDSCO to review and take necessary actions in a better way and would also ease the preparation of electronic submissions, which may happen in the near future at CDSCO.

New Drug Application

NDA is an application submitted to the FDA for permission to market a new drug. To obtain this permission a sponsor submits preclinical and clinical test data to NDA for analyzing the drug information, description of manufacturing procedures.

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 that is FDA formal review. At the conclusion of FDA 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 FDA provides applicant with an opportunity to meet with agency and discuss the deficiencies.[3,4]

Drug Controller General of India

Clinical Research is regulated 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. Matters related to product approval and standards, clinical trials, introduction of new drug, and import licenses of new drugs are handled by DCGI.[5]

Drugs Technical Advisory Board (DTAB)

It has technical experts and this advice the central and state governments on all technical 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 officials as members. Its main function is to ensure the drug control measures and enforce them uniformly over all the states.[4,5]

Genetic Engineering approval Committee (GEAC)

It is authority to approve r-DNA pharmaceuticals products. GEAC's role is to assess the bio-safety /environmental safety aspect of the biotechnological product.

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 of effectiveness and short term side effects
- **Phase III -** Confirmatory trial - Confirmation of therapeutic benefits
- **Phase IV -** Post marketing trial - Studies done after drug approval.[9-18]

Some of the rules & 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 Control Order 1995
- Consumer Protection Act-1986
- Factories Act-1948
- Law of Contracts (Indian contract Act-1872)
- Monopolistic & Restrictive Trade Practices Act-1969
- ICH GCP Guidelines
- Schedule Y Guidelines
- ICMR Guidelines
- Registry of Trial

Various Regulatory Agencies that are involved in drug regulation in India[4]:

- 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

- GEAC (Genetic Engineering Approval Committee): www.envfor.nic.in
- NPPA (National Pharmaceutical Pricing Authority): www.nppaindia.nic.in
- CBN-CCF: www.cbn.nic.in
- ICMR: www.icmr.nic.in
- Central Excise
- State Food & Drug Administration

Stages of approval[7,11]

1. Submission of Clinical Trial application for evaluating safety and efficacy.

2. Requirements for permission of new drugs approval.

3. Post approval changes in biological products: quality, safety and efficacy documents.

4. Preparation of the quality information for drug submission for new drug approval.

Figure 2: Flow chart for approval of drugs

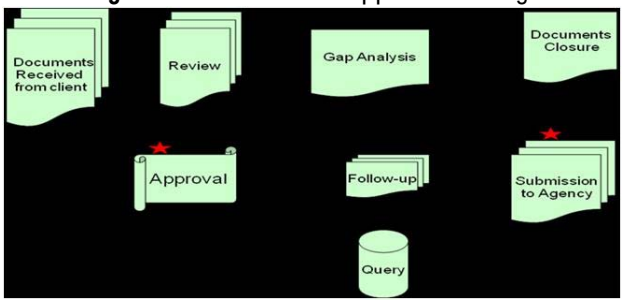
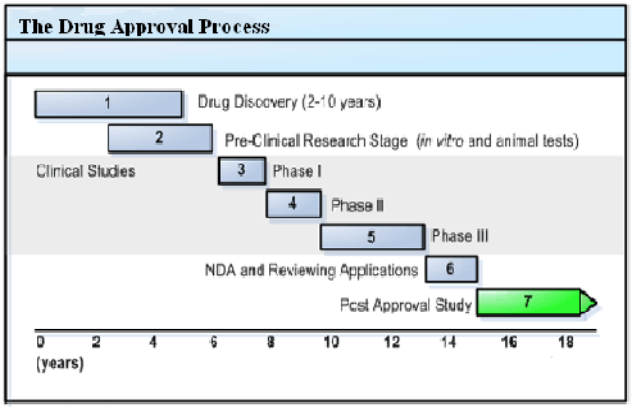


Figure 3: The drug approval process as a function of time



1. Submission of Clinical Trial Application for Evaluating Safety and Efficacy:

All the data listed below has to be produced.

(a) **Phase-I & phase- II clinical trial**:

- General information
  - Introduction about company: Brief description about company
  - Administrative headquarters: Provide address of company headquarters
  - Manufacturing Facilities: Provide address of company headquarters
  - Regulatory and intellectual property status in other countries.
  - Patent information status in India & other countries
- Chemistry manufacturing control
  - Product Description: A brief description of the drug and the therapeutic class to which it belongs.
  - Product Development
  - Strain details
  - Information on drug substance
  - Information on drug Product
- Non-clinical data: References: schedule – Y, amendment version 2005, Drugs and Cosmetics Rules, 1945
- Proposed phase-I / II studies: protocol for phase-I / II studies

(b) **Phase-III clinical trial:**

All the information is as same as phase-I & phase- II clinical trial

- General information
- Chemistry manufacturing control
- Non-clinical data
- Proposed phase-III studies

2. Requirements for permission of New Drugs Approval[5,8,9]

The manufacturer / sponsor have to submit application on Form 44 for permission of New Drugs Approval under the provisions of Drugs and Cosmetic Act 1940 and Rules 1945.

The document design is as per the International submission requirements of Common Technical Document (CTD) and has five Modules.

Module I*: *Administrative/Legal Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the region. The content and format of this module can be specified by the relevant regulatory authorities.

Module II*: *Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action and proposed clinical use. In general, the introduction should not exceed one page. The introduction should include proprietary name, non-proprietary name or common name of the drug

substance, company name, dosage form(s), strength(s), route of administration, and proposed indication(s). It contains the CTD summaries for quality, safety, efficacy information. This module is very important, as it provides detailed summaries of the various sections of the CTD. These include: A very short introduction. Quality overall summary, Non clinical overview, Clinical over view, Non clinical written and tabulated summaries for pharmacology, pharmacokinetics, and toxicology.

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

Information on quality should be presented in the structured format described in the guidance M4Q. This document is intended to provide guidance on the format of a registration application for drug substances and their corresponding drug 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

Information on safety should be presented in the structured format described in the guidance M4S. 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 relevant data, whether positive or negative, and should explain why and how the data support the proposed indication and prescribing information. It gives final copy of all of the final nonclinical study reports.

Module V: Clinical information

Information on efficacy should be presented in the structured format described in the guidance M4E. It gives clinical summary including biopharmaceutics, pharmacokinetics and pharmacodynamics, clinical pharmacology studies, clinical efficacy, clinical safety, synopses of the individual studies and final copy of detailed clinical study reports.[5,8,9]

3. Preparation 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) Appendices

- Facilities and equipment (name, manufacturer)
- Safety evaluation 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 [15]:

Application for permission to import New Drug (122-A):

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

b. An application for grant of permission to import a new drug shall be made in Form 44 to the Licensing Authority, accompanied by a fee of fifty thousand rupees:

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, is made, the fee to accompany such application shall be fifteen thousand rupees;

Provided further that any application received after one year of the grant of approval for the import and sale of new drug, shall be accompanied by a fee of fifteen thousand rupees and such information and data as required by Appendix 1 or Appendix 1A of Schedule Y, as the case may be.

2. The importer of a new drug when applying for permission under sub-rule (shall submit data as given in Appendix 1 to Schedule Y including the results of local clinical trials carried out in accordance with the guidelines specified in that Schedule and submit the report of such clinical trials in the format given in Appendix II to the said Schedule:

Provided that the requirement of submitting the results of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries:

Provided further that the submission of requirements relating to Animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

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

4. Provided that the Licensing Authority shall, where the data provided or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission, could be considered.[15]

Application for approval to manufacture New Drug other than the drugs classifiable under Schedules C and C (1) (122-B):

1. (**a)** No new drug shall be manufactured for sale unless it is approved by the Licensing Authority as defined in clause (b) of rule 21.

(b) An application for grant of approval to manufacture the new drug and its formulations shall be made in Form 44 to the Licensing Authority as defined in clause (b) of rule 21 and shall be accompanied by a fee of fifty thousand rupees;

Provided that where the application is for permission to import a new drug (bulk drug substance) and grant of approval to manufacture its formulation/s, the fee to accompany such application shall be fifty thousand rupees only;

Provided further that where a subsequent application by the same applicant for that drug, whether in modified dosage form or with new claims, is made, the fee to accompany such subsequent application shall be fifteen thousand rupees;

Provided further also that any application received after one year of the grant of approval for the manufacture for sale of the new drug, shall be accompanied by a fee of fifteen thousand rupees and such information and data as required by Appendix I or Appendix I A of Schedule Y, as the case may be.

2. The manufacturer of a new drug under sub-rule (1) when applying for approval to the licensing authority mentioned in the said sub-rule, shall submit data as given in Appendix I to schedule Y including the results of clinical trials carried out in the country in accordance with the guidelines specified in schedule Y and submit the report of such clinical trials in the format given in Appendix II to the said schedule.

The Licensing Authority as defined in clause (b) of rule 21 after being satisfied that the drug if approved to be manufactured as raw material (bulk drug substance) or as finished formulation shall be effective and safe for use in the country, shall issue approval in Form 46 and/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 or generated on the drug is inadequate, intimate the applicant in writing, and the conditions, which shall be satisfied before permission could be considered.

3. When applying for approval to manufacture of a new drug under sub-rule (1) or its preparations to the state licensing authority, an applicant shall produce along with his application, evidence that the drug for the manufacture of which application is made has already been approved by the licensing authority mentioned in Rule 21;

Provided that the requirement of submitting the result of local clinical trials may not be necessary if the drug is of such a nature that the licensing authority may, in public interest decide to grant such permission on the basis of data available from other countries;

Provided further that the submission of requirements relating to Animal toxicology, reproduction studies, teratogenic studies, perinatal studies, mutagenicity and Carcinogenicity may be modified or relaxed in case of new drugs approved and marketed for several years in other countries if he is satisfied that there is adequate published evidence regarding the safety of the drug, subject to the other provisions of these rules.

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

(1) An application for permission to import or manufacture fixed dose combination of two or more drugs 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 fee of fifteen thousand rupees and shall be accompanied by such information and data as is required in Appendix VI of Schedule Y.

(2) The Licensing Authority after being satisfied that the fixed dose combination, if approved to be imported or manufactured as finished formulation shall be effective and safe for use in the country, shall issue permission 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 provided or generated on the fixed dose combination is inadequate, intimate the applicant in writing, and the conditions which shall be satisfied before grant of approval/permission could be considered.

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

(1) No clinical trial for a new drug, whether for clinical investigation or any clinical experiment by any Institution, shall be conducted except under, and in accordance with, the permission, in writing, of the Licensing Authority defined in clause (b) of rule 21.

(2) An application for grant of permission to conduct,-

- Human clinical trials (Phase-I) on a new drug shall be made to the Licensing Authority 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 basis of data emerging from Phase-I trial, accompanied by a fee of twenty-five thousand rupees;
- Confirmatory clinical trials (Phase-III) on a new drug shall be made on the basis of the data

emerging from Phase-II and where necessary, data emerging from Phase-I also, and shall be accompanied by a fee of twenty-five thousand rupees:

Provided that no separate fee shall be required to be paid along with application for import/manufacture of a new drug based on successful completion of phases of clinical trials by the applicant.

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

(3) The Licensing Authority after being satisfied with the clinical trials, shall grant permission 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 applicant in writing, within six months, from the date of such intimation or such extended period, not exceeding a further period of six months, as the Licensing Authority may, for reasons to be recorded, in writing, permit, intimating the conditions which shall be satisfied before permission could be considered:

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

If the importer or manufacturer under this Part fails 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 reasons there for, suspend or cancel it.

Appeal (122-DC)

Any person aggrieved by an order passed by the Licensing Authority under 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 necessary, may pass such order in relation thereto as it thinks fit.[1-4]

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 requirements along with the NDA to FDA.

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 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 **122 A, 122 B, 122 D,** and **122 DA.**

REFERENCES

1. Clinical Trial & Global Clinical Trial. Available at http://cdsco.nic.in/clinical_trial.htm Accessed on AUG 19, 2011.
2. The New Drug Approval Process. Available at http://www.fda.gov/cder/handbook. Accessed on AUG 19, 2011.
3. CDER Guidance: IND application process (interactive session). A review for OCRA US RAC Study. www.fda.gov/cder/regulatory/applications/ind_page_1. htm Accessed on AUG 25, 2011.
4. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Med. J. Aust. 181, 2004, 293-94.
5. Guidance for industry on preparation of common technical document for import/ manufacture and marketing approval of new drugs for human use. (NEW DRUG APPLICATION – NDA). Available at http://cdsco.nic.in/CTD_Guidance%20-Final.pdf. Accessed on AUG 25, 2011.
6. Honorio S. Phases of drug development; Good practices in clinical research. Available at: www.hstelearning.mit.edu. Accessed on AUG 26, 2011
7. Ravinder RB & Suresh N, Regulatory stages for New Drug approvals. Available at www.observerindia.com/cms/export/orfonline/modules /occasionalpaper/attachments/Drug_Discovery_Book_1 260179432814.pdf. Accessed on AUG 28, 2011.
8. Lachman L, Liberman HA, Kanig JL, The Theory and Practice of Industrial Pharmacy, Varghese Publishing House, 3rd edition 1987. 856-82.
9. Kuhlmann J, Alternative strategies in drug development: clinical pharmacological aspects. Int. J. Clin. Pharmacol. Ther. 37(12), 1999, 575-83.
10. The drug development and approval process. Available at: www.mhsource.com/resource/process.html. Accessed on SEP 03, 2011.
11. Bhatt A. Clinical trials in India: Pangs of globalization. Indian J. Pharmacol. 36(4), 2004, 207 -08.
12. Investigational New Drug Application (IND) Available at www1.pointcross.com/source/ddg/steps/ind/index.html Accessed on SEP 05, 2011.
13. Lee K, Bacchetti P, Sim I. Publication of Clinical Trials Supporting Successful New Drug Applications: A Literature Analysis. PLoS Med. 5(9), 2008, 191-194.
14. Dulichand R, Harish D. New Drug Approval Process: Regulatory View. Available at www.pharmainfo.net/ reviews/new-drug-approval-process-regulatory-view. Accessed on SEP 05, 2011.
15. Tharyan P. Prospective Registration of Clinical Trials in India: Strategies, Achievements & Challenges. J. Evidence. Med. 2(1), 2009, 19-28.

16. Davina G, Prathap T. Registering clinical trials in India: A scientific and ethical imperative. National Med. J. India. 21(1), 2008, 31-34.

17. Mohanan Nair V, Martin DK. Concerns about ethical review of health research in India. Indian J. Med. Ethics. 1, 2004, 119–20.

18. Nundy S, Gulhati CM. A new colonialism-Conducting clinical trials in India. N. Eng. J. Med. 352, 2005, 1633–6.

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