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CURRENT REGULATIONS FOR CLINICAL TRIALS

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Abstract:
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 and USA.

Keywords: *Drug approval process, Clinical trials, marketing.*

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INTRODUCTION TO REGULATORY AFFAIRS IN PHARMACEUTICAL INDUSTRY:

Introduction to regulatory affairs:

Regulatory affairs (ra), also called government affairs, is a profession within regulated industries, such as pharmaceuticals, medical devices, energy, and banking. Regulatory affairs also has a very specific meaning within the healthcare industries (pharmaceuticals, medical devices, biologics and functional foods). Most companies, whether they are major multinational pharmaceutical corporations or small, innovative biotechnology companies, have specialist departments of regulatory affairs professionals. The success of regulatory strategy is less dependent on the regulations than on how they are interpreted, applied, and communicated within companies and to outside constituents.

This department is responsible for knowing the regulatory requirements for getting new products approved. They know what commitments the company has made to the regulatory agencies where the product has been approved. They also submit annual reports and supplements to the agencies. Regulatory affairs typically communicate with one of the centers (e.g., center for drug evaluation and research) at the fda headquarters, rather than the fda local district offices. Gimps do not directly apply to regulatory affairs; however, they must understand and evaluate changes to drug manufacturing and testing activities to determine if and when the fda must be notified.

IMPORTANCE OF REGULATORY AFFAIRS

In today's competitive environment the reduction of the time taken to reach the market is critical to a product's and hence the company's success. The proper conduct of its regulatory affairs activities is therefore of considerable economic importance for the company.

Inadequate reporting of data may prevent a timely positive evaluation of marketing application. A new drug may have cost many millions of pounds, euros or dollars to develop and even a three-month delay in bringing it to the market has considerable financial considerations. Even worse1 failures to fully report all the available data or the release of product bearing incorrect labeling, may easily result in the need for a product recall. Either occurrence may lead to the loss of several millions of units of sales, not to mention the resulting reduction in confidence of the investors, health professionals and patients.

A good regulatory affairs professional will have a 'right first time' approach and will play a very important part in coordinating scientific endeavor with regulatory demands throughout the life of the product, helping to maximize the cost-effective use of the company's resources.

The regulatory affairs department is very often the first point of contact between the government authorities and the company. The attitudes and actions of the regulatory affairs professionals will condition the perceptions of the government officials to the company for better, or worse officials respond much better to a company whose representatives are scientifically accurate and knowledgeable than to one in which these qualities are absent.

The importance of the regulatory affairs function is such that senior regulatory affairs professionals are increasingly being appointed to boardroom positions, where they can advise upon and further influence the strategic decisions of their companies.

4.AIM & OBJECTIVES

This Study provides detailed guidance on general drug approval process in India.

Assessing national medicines regulatory systems National Medicines Regulatory Authorities (MRAs) are responsible for the regulation and control of medical products such as medicines, vaccines, blood products and medical devices.

They contribute to promoting and protecting public health by ensuring that:

- Medicines are of the required quality, safety and efficacy,
- Health professionals and patients have the necessary information to enable them to use medicines rationally,
- Medicines are appropriately manufactured, stored, distributed and dispensed,
- Illegal manufacturing and trade are detected and adequately sanctioned,
- Promotion and adverting is fair, balanced and aimed at rational drug use,
- Access to medicines is not hindered by unjustified regulatory work.

Intensification of international commerce and increasing technological complexity of manufacturing and product specifications have created additional challenges for national regulatory authorities and manufacturers, particularly to those of developing countries. This requires that national regulatory capacity is regularly assessed, areas of weakness are identified and appropriate, necessary measures are taken. Assessments are conducted using a standardized WHO Data Collection Tool for the review of Drug regulatory Systems.

DISCUSSION

The new drug approval is of two phase process the first phase for clinical trials and second phase for

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

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

DRUG APPROVAL PROCESS IN INDIA

1) investigation of new drug in India

Current Federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will probably want to ship the investigational drug to clinical investigators in many states, it must seek an exemption from that legal requirement. The IND is the means through which the sponsor technically obtains this exemption from the FDA.

During a new drug's early preclinical development, the sponsor's primary goal is to determine if the product is reasonably safe for initial use in humans, and if the compound exhibits pharmacological activity that justifies commercial development. When a product is identified as a viable candidate for further development, the sponsor then focuses on collecting the data and information necessary to establish that the product will not expose humans to unreasonable risks when used in limited, early-stage clinical studies.

FDA's role in the development of a new drug begins when the drug's sponsor (usually the manufacturer or potential marketer) having screened the new molecule for pharmacological activity and acute toxicity potential in animals, wants to test its diagnostic or therapeutic potential in humans. At that point, the molecule changes in legal status under the Federal Food, Drug, and Cosmetic Act and becomes a new drug subject to specific requirements of the drug regulatory system.

The IND application must contain information in three broad areas:

Animal Pharmacology and Toxicology Studies - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included are any previous experience with the drug in humans (often foreign use).

Manufacturing Information - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

Clinical Protocols and Investigator Information - Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks. Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk.

2) Procedure for new drug approval in India

The Drug and Cosmetic Act 1940 and Rules 1945 were passed by the India's parliament to regulate the import, manufacture, distribution and sale of drugs and cosmetics. The Central Drugs Standard Control Organization (CDSCO), and the office of its leader, the Drugs Controller General (India) [DCGI] 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 10 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.

The drug approval process varies from one country to another. In some countries, only a single body regulates the drugs and responsible for all regulatory task such as approval of new drugs, providing license for manufacturing and inspection of manufacturing plants e.g. in USA, FDA performs all the functions. However in some counties all tasks are not performed by a single regulatory authority, such as in India, this responsibility is divided on Centralized and State authorities. Other issues where the difference appears are, time taken for the approval of a CTA application, time taken in evaluation of marketing authorization application, registration fee, registration process and marketing exclusivity .

Some counties have two review processes as normal review process and accelerated review process as in USA, China etc. and some countries have only a single review process as in India. Similarly, the format used for the presentation of dossier submitted for approval of drug is also different. In some countries like as in USA, EU, and Japan , it is mandatory that the dossier prepared in CTD format, however, in some countries it is optional such as in India

IND-Investigational New Drug, DCGI-Drug Controller General of India, CDSCO-Centre for Drug Standards Control organization.

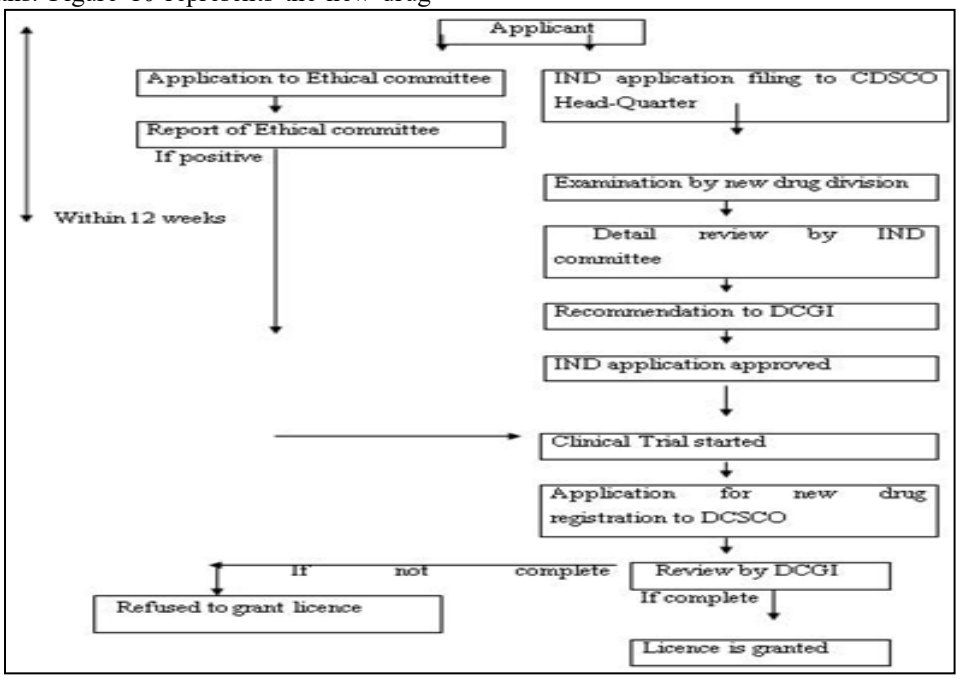


Figure : New Drug Registration Process of India

CTD GUIDELINE IN INDIA:

Scope:

This guideline applies to import / manufacture and marketing approval of new drugs including New chemical entity, new indication, new dosage forms, modified release form, new route of administration etc. under the definition of new drug under Rule 122E of Drugs & Cosmetics rules as a finished pharmaceutical product.

What is CTD?

The CTD is only a format for submission of information to CDSCO. It does not define the content.

Difference in organization of data in each application has made reviewing more difficult and can also lead to omission of critical data or analysis so unnecessary delay in approval. Thus common format of submission will help. Through the ICH process, CTD guidance developed for japan,EU & US. CDSCO also adopted the CTD.

Guidelines for preparation of CTD

CTD: over view

Module 1: General Information

This module should contain documents specific to India; for example, Form 44, Treasury challan fee or the proposed label for use in India.

1) Covering letters & comprenshive table of contents (module 1 to 5)
2) Administrative information

- Brief introduction about the applicant company
- Duly filled and signed application form 44 and treasury challan
- Legal and critical documents
- Coordinates related to the application
- General information of the drug product
- Summary of the testing protocol(s) for quality control testing
- Regulatory status in other countries
- Domestic price of the drug followed in the countries of origin
- Brief profile of manufacturer's company & business activity
- Information regarding involvement of expert if any
- Samples of drug product
- Promotional material

Module 2: CTD Summaries

This module should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use, not exceeding one page. Module 2 should contain 7 sections in the following order:

1) CTD table of contents
2) CTD introduction
3) Quality overall summary
4) Nonclinical overview
5) Clinical overview
6) Nonclinical written and tabulated summaries
7) Clinical summary

In this module following information is required

1) Table of content of module
2) Introduction
3) Quality overall summary

In this section not provide the entire information it is presented in module 3. It is not more than 40 pages.

4) Summary of drug substance & drug product
5) Nonclinical overview
6) Clinical over view

MODULE:3 quality

In this module following information is required

1) Table of contents of module 3
2) Drug substances
3) Manufacture of drug substances
4) Characterization of drug substances
5) Quality control of drug substances
6) Reference standards and material
7) Container closer system
8) Stability of drug substance
9) Drug product and manufacture of drug product
10) Control of drug product and excipient

MODULE:4 non clinical study report

Table of contents in this module should be provided that lists all of the nonclinical study reports and gives the location of the each study reports in CTD.

It contains following data

1) study reports

- Pharmacology
- Pharmacokinetic
- Toxicology

2) literature references

MODULE: 5 Clinical study report

It contains tabular listing of all clinical studies. Following data are required

1) Clinical study report

- Reports of biopharmaceutical studies
- Reports of studies pertinent to pharmacokinetic using human biomaterials.
- Reports of human pharmacokinetic studies
- Reports of human pharmacodynamic studies
- Reports of efficacy and safety study
- Reports of post marketing experience
- Case report form and individual patient listing
- Literature references [CDSCO Guideline]

DOCUMENTS TO BE SUBMITTED FOR GRANT OF PERMISSION TO CONDUCT BIOEQUIVALENCE STUDIES FOR EXPORT PURPOSE:

A large number of applications are being filed to the office of DCG (I) at CDSCO (HQ) by Pharmaceutical companies, both manufacturers and importers as well as CRO's on behalf of them, requesting for the approval to carry out BE studies

with various pharmaceutical dosage formulations on Indian subjects.

In light of the above, for easy processing of such applications and to bring uniformity in decision making all stake holders of the afore mentioned activities are hereby advised to submit their applications with following documents. All applications should accompany the documents with proper index & page number.

New Drugs – developed in India as an IND and not marketed anywhere in world.

1. Form 44
2. Treasury Challan of INR 50,000.
3. Source of bulk drugs /raw materials.

Requirements for BE study of a new molecule not approved in India but approved in the other countries:

1. Application in Form-44 duly signed, by the competent authority with name and designation.
2. Treasury Challan of Rs. 50000/- as per Drugs & Cosmetic Rules.
3. Undertaking by the Principal Investigator (PI) as per appendix VII of schedule "Y" of Drugs and Cosmetic Rules.
4. A copy of the approval granted to the BE study centre by CDSCO.
5. Sponsor's Authorization letter duly signed by the competent authority on their letterhead.
6. The study protocols.
7. The study synopsis
8. Pre-clinical single dose data and repeated dose toxicity data.
9. Clinical study data and published report of pharmacokinetic and pharmacodynamic study carried out in healthy volunteers/patients data published in reputed journals.
10. Regulatory status of the drug.
11. Names of the countries where the drug is currently being marketed (to be mentioned in the covering letter also).
12. Package literature on the international product
13. Complete Certificate of Analysis of same batches (both test & reference formulations) to be used in the BE study.
14. In the case of multiple dose BE study adequate supporting safety data should be submitted.
15. In the case of Injectable preparation the sub-acute toxicity should be submitted on the product of the sponsor, generated in two species for adequate duration.
16. Depending on the nature of the drug like cytoxic agent, hormonal preparations etc. Proper justification for conducting studies on healthy volunteers/patients or male/ female should be submitted.

New Drugs approved in India within period of 1 year:

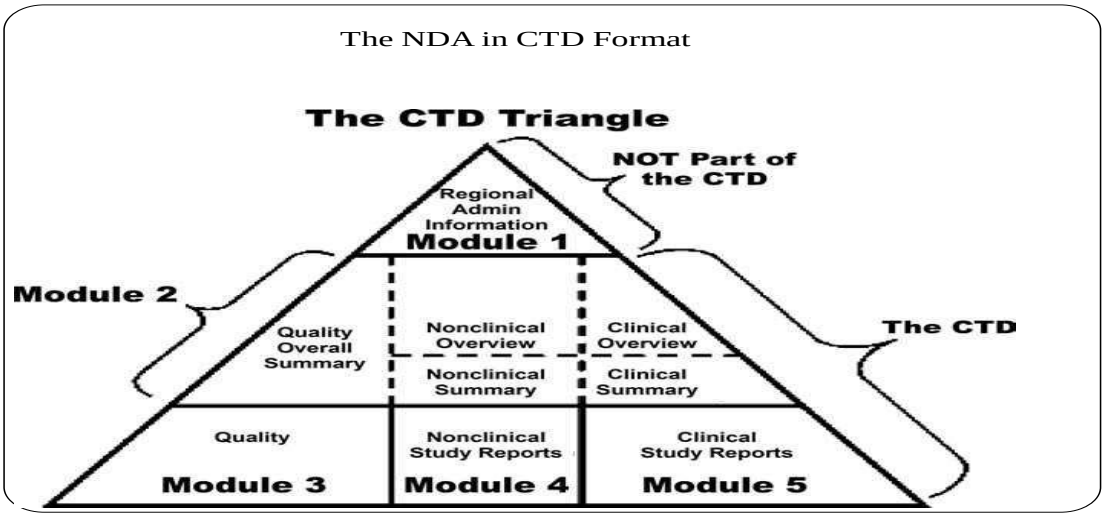
1. Application in Form-44 duly signed, by the competent authority with name and designation
2. Treasury Challan of Rs. 25000/- as per Drugs & Cosmetic Rules.
3. Undertaking by the Principal Investigator (PI) as per appendix VII of schedule "Y" of Drugs and Cosmetic Rules.
4. A copy of the approval of the BE study centre from CDSCO.
5. Sponsor's Authorization letter duly signed by the competent authority on their letterhead.
6. The study protocols.
7. Clinical study data and published report of pharmacokinetic and pharmacodynamic study carried out in healthy volunteers data published in reputed journals.
8. Package literature on the international product.
9. Complete Certificate of Analysis of same batches (both test & reference formulations) to be used in the BE study.
10. In the case of multiple dose BE study adequate supporting safety data should be submitted.
11. In the case of Injectable preparation the sub-acute toxicity should be submitted on the product of the sponsor, generated in two species for adequate duration.
12. Depending on the nature of the drug like cytoxic agent, hormonal preparations etc. Proper justification for conducting studies on healthy volunteers/patients or male/ female should be submitted.

New Drugs approved within period of more than 1 year & less than 4 years:

1. Application in Form-44 duly signed, by the competent authority with name and designation
2. Treasury Challan of Rs. 15000/- as per Drugs & Cosmetic Rules.
3. Undertaking by the Principal Investigator (PI) as per appendix VII of schedule "Y" of Drugs and Cosmetic Rules.
4. A copy of the approval of the BE study centre from CDSCO.
5. Sponsor's Authorization letter duly signed on their letterhead by the competent authority.
6. The study protocols.
7. Complete Certificate of Analysis of same batches (both test & reference formulations) to be used in the BE study.
8. In the case of multiple dose BE study adequate supporting safety data should be submitted.
9. In the case of Injectable preparation the sub-acute toxicity should be submitted on the product of the sponsor, generated in two species for adequate duration.
10. Depending on the nature of the drug like cytoxic agent, hormonal preparations etc. Proper justification for conducting studies on healthy volunteers/patients or male/ female should be submitted.

BE NOC for all the drug products in modified release form irrespective of their approval status:

1. Application in Form-44 duly signed, by the competent authority with name and designation
2. Treasury Challan of Rs. 15000/- as per Drugs & Cosmetic Rules.
3. Undertaking by the Principal Investigator (PI) as per appendix VII of schedule "Y" of Drugs and Cosmetic Rules.
4. A copy of the approval of the BE study centre from CDSCO.
5. Sponsor's Authorization letter duly signed on their letterhead by the competent authority.
6. The study protocols.
7. Complete Certificate of Analysis of same batches (both test & reference formulations) to be used in the BE study.
8. In the case of multiple dose BE study adequate supporting safety data should be submitted.
9. In the case of Injectable preparation the sub-acute toxicity should be submitted on the product of the sponsor, generated in two species for adequate duration.
10. Depending on the nature of the drug like cytoxic agent, hormonal preparations etc. Proper justification for conducting studies on healthy volunteers/patients or male/ female should be submitted.



APPLICATION FORM FORMAT:

Form 44 (INDIA) (See rules 122 A, 122 B, 122 D, and 122 DA)

Application for grant of permission to import or manufacture a New Drug or to undertake clinical trial.

*****

I/we_____ of M/s. _____(address)

hereby apply for grant of permission for import of and/or clinical trial or for approval to manufacture a new drug or fixed dose combination or subsequent permission for already approved new drug. The necessary information / data is given below:

1.Particulars of New Drug:

(1) Name of the drug:
(2) Dosage Form:
(3) Composition of the formulation:
(4) Test specification:
(i) active ingredients:
(ii) inactive ingredients:
(5) Pharmacological classification of the drug:
(6) Indications for which proposed to be used:
(7) Manufacturer of the raw material (bulk drug substances):
(8) Patent status of the drug:

2. Data submitted along with the application (as per Schedule Y with indexing and page nos.)

A. Permission to market a new drug :-

(1) Chemical and Pharmaceutical information
(2) Animal Pharmacology

(3) Animal Toxicology
(4) Human/Clinical Pharmacology (Phase I)
(5) Exploratory Clinical Trials (Phase II)
(6) Confirmatory Clinical Trials (Phase III) (including published review articles)
(7) Bio-availability, dissolution and stability study Data
(8) Regulatory status in other countries
(9) Marketing information:
(a) Proposed product monograph
(b) Drafts of labels and cartons
(10) Application for test license

B. Subsequent approval / permission for manufacture of already approved new drug

(a) Formulation:

(1) Bio-availability/ bio-equivalence protocol
(2) Name of the investigator/center
(3) Source of raw material (bulk drug substances) and stability study data.

(b) Raw material (bulk drug substances)

(1) Manufacturing method
(2) Quality control parameters and/or analytical specification, stability report.
(3) Animal toxicity data

C. Approval / Permission for fixed dose combination:

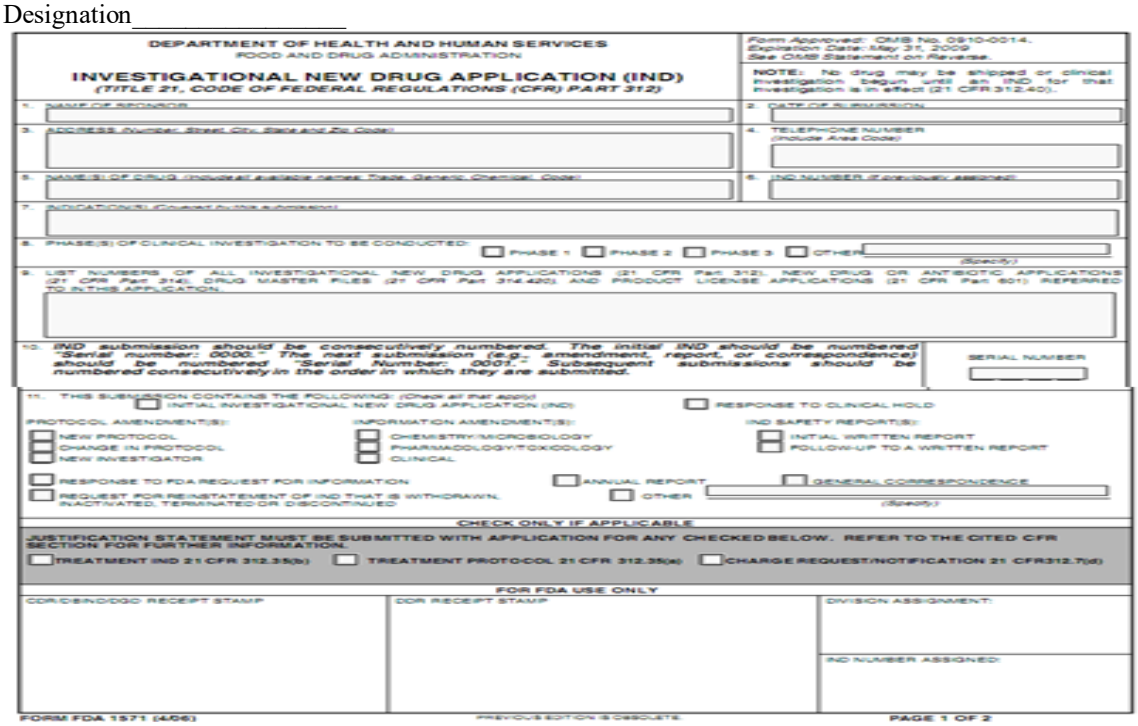
(1) Therapeutic Justification (authentic literature in pre-reviewed journals/text books)
(2) Data on pharmacokinetics/ pharmacodynamics combination
(3) Any other data generated by the applicant on the safety and efficacy of the combination.

D. Subsequent Approval or approval for new indication – new dosage form:

(1) Number and date of Approval/permission already granted.
(2) Therapeutic Justification for new claim / modified dosage form.
(3) Data generated on safety, efficacy and quality parameters.

A total fee of rupees_____ (in words)._____) has been credited to the Government under the Head of Account_____ (Photocopy of receipt is enclosed).

Dated_____
Signature_____
Designation_____



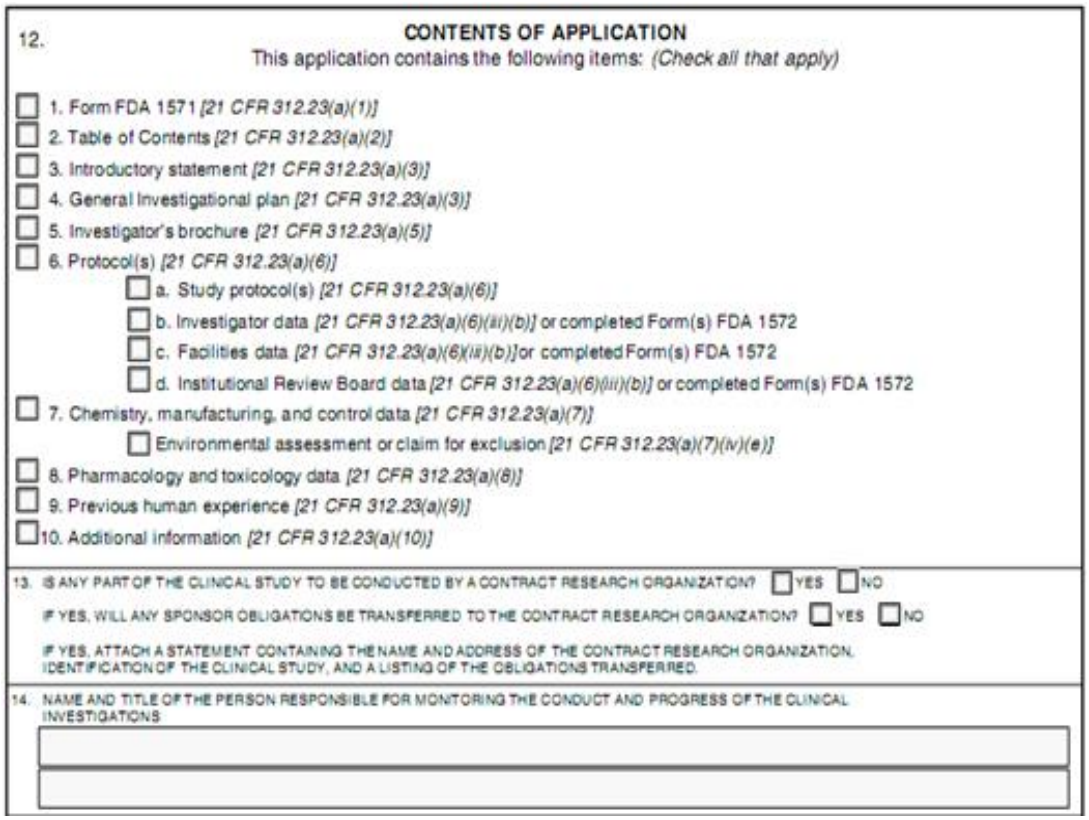
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

Form Approved: OMB No. 0910-0014.
Expiration Date: May 31, 2009
See OMB Statement on Reverse.

NOTE: No drug may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40).

1. NAME OF SPONSOR
2. DATE OF SUBMISSION
3. ADDRESS (Number, Street, City, State and Zip Code)
4. TELEPHONE NUMBER (Include Area Code)
5. NAME(S) OF DRUG (Include all available names: Trade, Generic, Chemical, Code)
6. IND NUMBER (If previously assigned)
7. INDICATION(S) (Covered by this submission)
8. PHASE(S) OF CLINICAL INVESTIGATION TO BE CONDUCTED: ☐ PHASE 1 ☐ PHASE 2 ☐ PHASE 3 ☐ OTHER (Specify)
9. LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), DRUG MASTER FILES (21 CFR Part 314.420), AND PRODUCT LICENSE APPLICATIONS (21 CFR Part 601) REFERRED TO IN THIS APPLICATION
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted. SERIAL NUMBER
11. THIS SUBMISSION CONTAINS THE FOLLOWING: (Check all that apply)
☐ INITIAL INVESTIGATIONAL NEW DRUG APPLICATION (IND) ☐ RESPONSE TO CLINICAL HOLD
PROTOCOL AMENDMENT(S): ☐ NEW PROTOCOL ☐ CHANGE IN PROTOCOL ☐ NEW INVESTIGATOR
INFORMATION AMENDMENT(S): ☐ CHEMISTRY/MICROBIOLOGY ☐ PHARMACOLOGY/TOXICOLOGY ☐ CLINICAL
IND SAFETY REPORT(S): ☐ INITIAL WRITTEN REPORT ☐ FOLLOW-UP TO A WRITTEN REPORT
☐ RESPONSE TO FDA REQUEST FOR INFORMATION ☐ ANNUAL REPORT ☐ GENERAL CORRESPONDENCE
☐ REQUEST FOR REINSTATEMENT OF IND THAT IS WITHDRAWN, INACTIVATED, TERMINATED OR DISCONTINUED ☐ OTHER (Specify)
CHECK ONLY IF APPLICABLE
JUSTIFICATION STATEMENT MUST BE SUBMITTED WITH APPLICATION FOR ANY CHECKED BELOW. REFER TO THE CITED CFR SECTION FOR FURTHER INFORMATION.
☐ TREATMENT IND 21 CFR 312.35(b) ☐ TREATMENT PROTOCOL 21 CFR 312.35(a) ☐ CHARGE REQUEST/NOTIFICATION 21 CFR312.7(d)
FOR FDA USE ONLY
CDR/CBER/OCBQ RECEIPT STAMP
CDR RECEIPT STAMP
DIVISION ASSIGNMENT
IND NUMBER ASSIGNED
FORM FDA 1571 (4/06) PREVIOUS EDITION IS OBSOLETE. PAGE 1 OF 2



12. CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

- ☐ 1. Form FDA 1571 *[21 CFR 312.23(a)(1)]*
- ☐ 2. Table of Contents *[21 CFR 312.23(a)(2)]*
- ☐ 3. Introductory statement *[21 CFR 312.23(a)(3)]*
- ☐ 4. General investigational plan *[21 CFR 312.23(a)(3)]*
- ☐ 5. Investigator's brochure *[21 CFR 312.23(a)(5)]*
- ☐ 6. Protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ a. Study protocol(s) *[21 CFR 312.23(a)(6)]*
  - ☐ b. Investigator data *[21 CFR 312.23(a)(6)(ii)(b)]* or completed Form(s) FDA 1572
  - ☐ c. Facilities data *[21 CFR 312.23(a)(6)(ii)(b)]* or completed Form(s) FDA 1572
  - ☐ d. Institutional Review Board data *[21 CFR 312.23(a)(6)(iii)(b)]* or completed Form(s) FDA 1572
- ☐ 7. Chemistry, manufacturing, and control data *[21 CFR 312.23(a)(7)]*
  - ☐ Environmental assessment or claim for exclusion *[21 CFR 312.23(a)(7)(iv)(e)]*
- ☐ 8. Pharmacology and toxicology data *[21 CFR 312.23(a)(8)]*
- ☐ 9. Previous human experience *[21 CFR 312.23(a)(9)]*
- ☐ 10. Additional information *[21 CFR 312.23(a)(10)]*

13. IS ANY PART OF THE CLINICAL STUDY TO BE CONDUCTED BY A CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, WILL ANY SPONSOR OBLIGATIONS BE TRANSFERRED TO THE CONTRACT RESEARCH ORGANIZATION? ☐ YES ☐ NO

IF YES, ATTACH A STATEMENT CONTAINING THE NAME AND ADDRESS OF THE CONTRACT RESEARCH ORGANIZATION, IDENTIFICATION OF THE CLINICAL STUDY, AND A LISTING OF THE OBLIGATIONS TRANSFERRED.

14. NAME AND TITLE OF THE PERSON RESPONSIBLE FOR MONITORING THE CONDUCT AND PROGRESS OF THE CLINICAL INVESTIGATIONS

Table . Comparison of Drug approval process.

Country	Time for Regulatory Approval of CTA/IND Application	Time for Evaluation of MAA	MAA Fee
Australia	120 day	50 days	$192,400
China	50 days	180 days	DNA
India	16-18 weeks	8-12 weeks	50,000 INR
UK	35 days	210 days	£254100
USA	30 days	180 days	$217,787

Drug Approval Process In USA

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

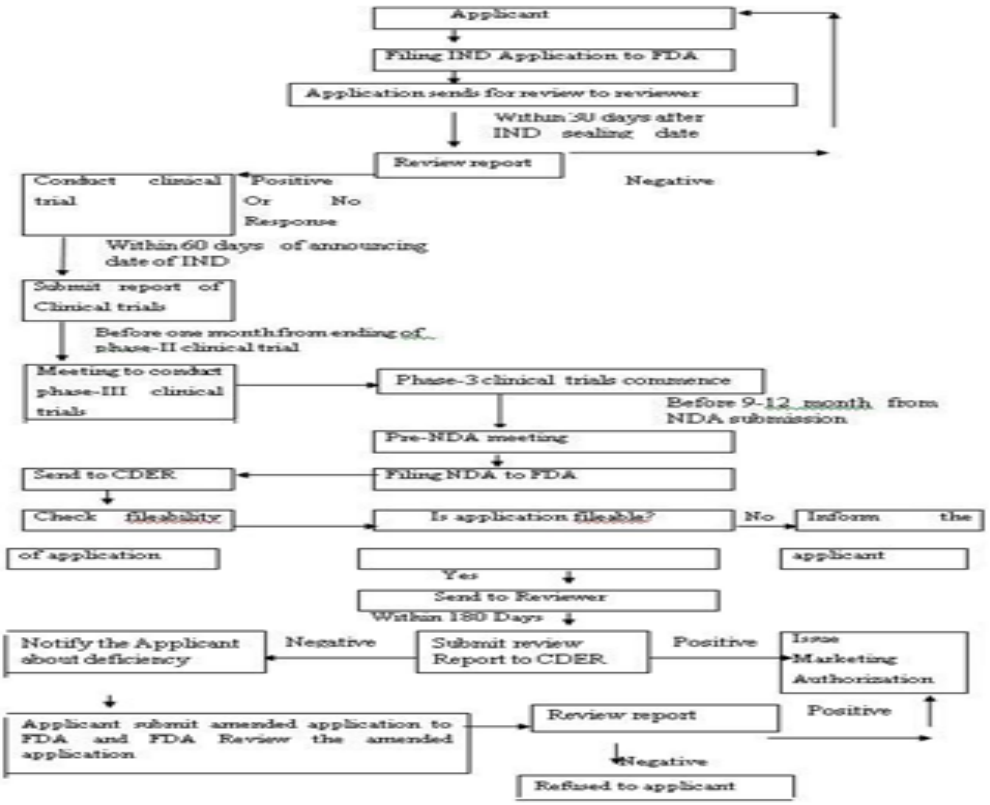
The Food and Drug Administration (FDA or USFDA) is an agency of the United States Department of Health and Human Services and is responsible for regulating and supervising the safety of foods, dietary supplements, drugs, vaccines,

biological medical products, blood products, medical devices, radiation-emitting devices, veterinary products, and cosmetics.

The Food and Drug Administration (FDA) is responsible for protecting and promoting public health. Like general drug approval process, FDA's new drug approval process is also accomplished in two phases: clinical trials (CT) and new drug application (NDA) approval. FDA approval process begins only after submission of investigational new drug (IND) application. The IND application should provide high quality preclinical data to justify the testing of the drug in humans. Almost 85% of drugs are subjected to clinical trials, for which IND applications are filed. The next step is phase-I clinical trials (1-3 years) on human subjects (~100). The drug's safety profile and pharmacokinetics of drug are focused in this phase. Phase II trials (2 years) are performed if the drug successfully passes phase I. To evaluate dosage, broad efficacy and additional safety in people (~300) are the main objective of the phase II. If evidence of effectiveness is shown in phase II, phase III studies (3-4 years) begins. These phase III concerns more about safety and effectiveness of drug from data of different populations, dosages and its combination with other drugs in several hundred to about 3,000 peoples. A new drug application (NDA) can be filed only when the drug successfully passes all three phases of clinical trials and includes all animal and human data, data analyses, pharmacokinetics of drug and its manufacturing and proposed labelling. The preclinical, clinical reports and risk-benefit analysis (product's beneficial effects outweigh its possible harmful effects) are reviewed at the Center for Drug Evaluation and Research by a team of scientists. Generally approval of an NDA is granted within two years (on an average), however, this process can be completed from two months to several years. The innovating company is allowed to market the drug after the approval of an NDA and is considered to be in Phase IV trials. In this phase, new areas, uses or new populations, long-term effects, and how participants respond to different dosages are explored. Figure represents the new drug approval process of FDA.

IND-Investigational New Drug, FDA-Food and Drug Administration, NDA-New Drug Application, CDER-Centre for Drug Evaluation and Research

Figure : New Drug Application Approval Process of FDA



FDA-Organizations

- The Office of the Commissioner (OC)
- The Center for Drug Evaluation and Research (CDER)
- The Center for Biologics Evaluation and Research (CBER)
- The Center for Food Safety and Applied Nutrition (CFSAN)
- The Center for Devices and Radiological Health (CDRH)
- The Center for Veterinary Medicine (CVM)

- The National Center for Toxicological Research (NCTR)
- The Office of Regulatory Affairs (ORA)
- Office of Criminal Investigations (OCI)

CONCLUSION:

Generally, the drug approval process comprised mainly the two steps, application to conduct clinical trial and application to the regulatory authority for marketing authorization of drug. The new drug approval process of various countries is similar in some of the aspects whereas it differs in some aspects. In most of the counties, sponsor firstly files an application to conduct clinical trial, and only after the approval by the regulatory authority, the applicant conducts the clinical studies and further submits an application to the regulatory authority for marketing authorization of drug. In all countries, information submitted to regulatory authorities regarding the quality, safety and efficacy of drug is similar; however, the time, fee and review process of clinical trials and marketing authorization application differs. For the purpose of harmonisation, the International Conference on Harmonisation (ICH) has taken major steps for recommendations in the uniform interpretation and application of technical guidelines and requirements. This step will ultimately reduce the need to duplicate work carried out during the research and development of new drugs. Therefore, harmonization of drug approval processes either by ICH or WHO may be initiated at global level.

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