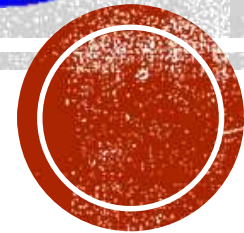


# REGULATORY REQUIREMENTS FOR DRUG PRODUCT



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# WHY???

- **Thalidomide catastrophe (1962)**

Phocomelia(malformation of limbs)

10,000 cases reported worldwide, 50% survived

- **Elixir sulphonamide(1937)**

Diethylene glycol known toxin was used as solvent

More than 100 death

- Such tragic incidents led to introduction of regulations for approval of new drugs

## INTRODUCTION

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

# REGULATORY ORGANIZATIONS IN COUNTRIES

- USFDA (United States)
- CDSCO - Central drugs standard control organization (India)
- EMEA - European Agency for the evaluation of medicinal products (European Union)
- MoH (Sri Lanka)
- DDA - Department of drug Administration (Nepal)



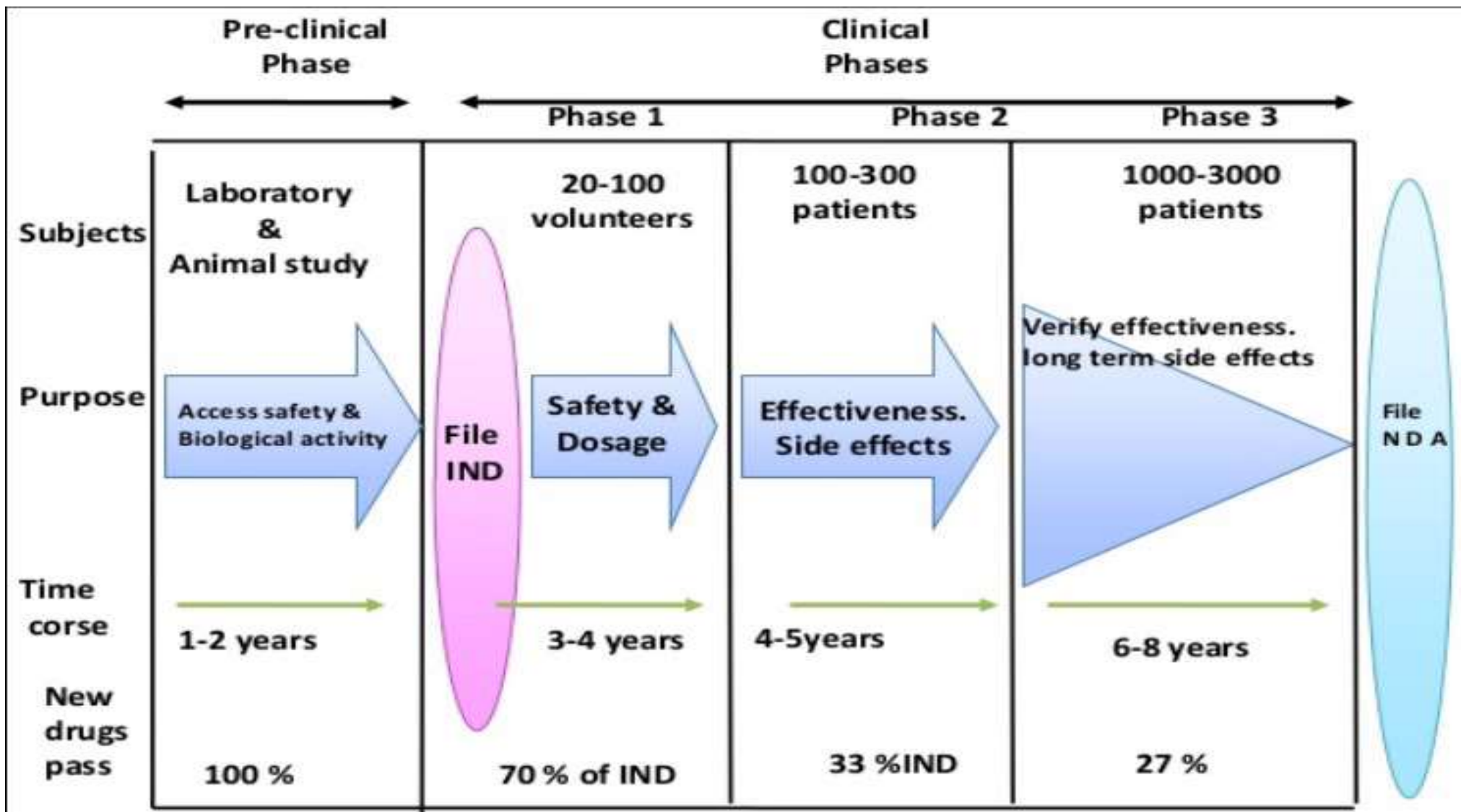
# DRUG APPROVAL PROCESS IN USA

In 1820, the new era of USA drug regulation was started with the establishment of US 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.

# DIFFERENT TYPES OF DRUG APPLICATIONS THAT CAN BE SUBMITTED TO FDA

- IND(investigational new drug application)
- NDA(new drug application)
- ANDA( abbreviated new drug application)
- BLA(biologic license Application)

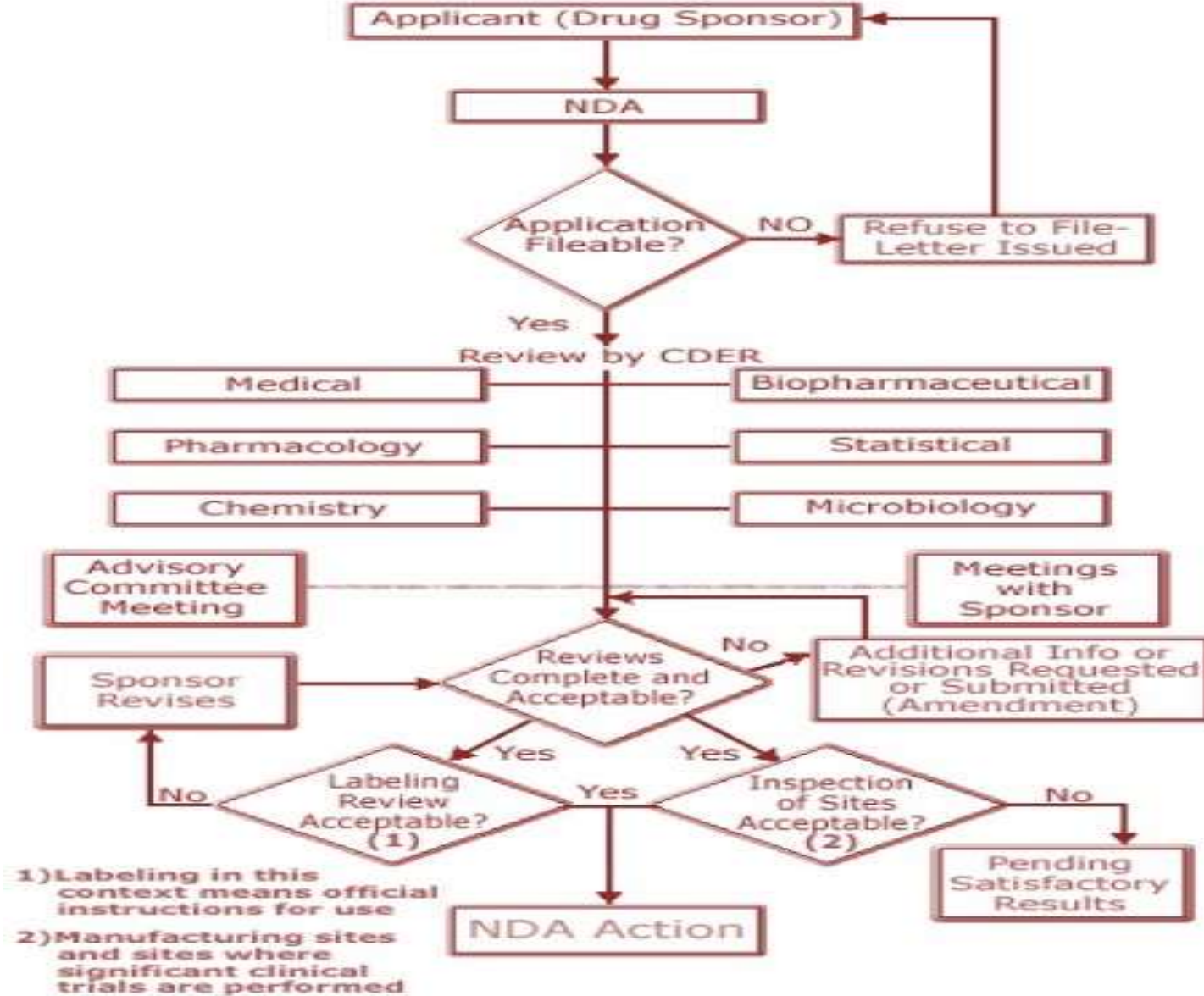
- The Food and Drug Administration (FDA) is responsible for protecting and promoting public health.
- FDA's new drug approval process is also accomplished in two phases: **clinical trials (CT)** and **new drug application (NDA) approval**. FDA approval process begins only after submission of **investigational 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.

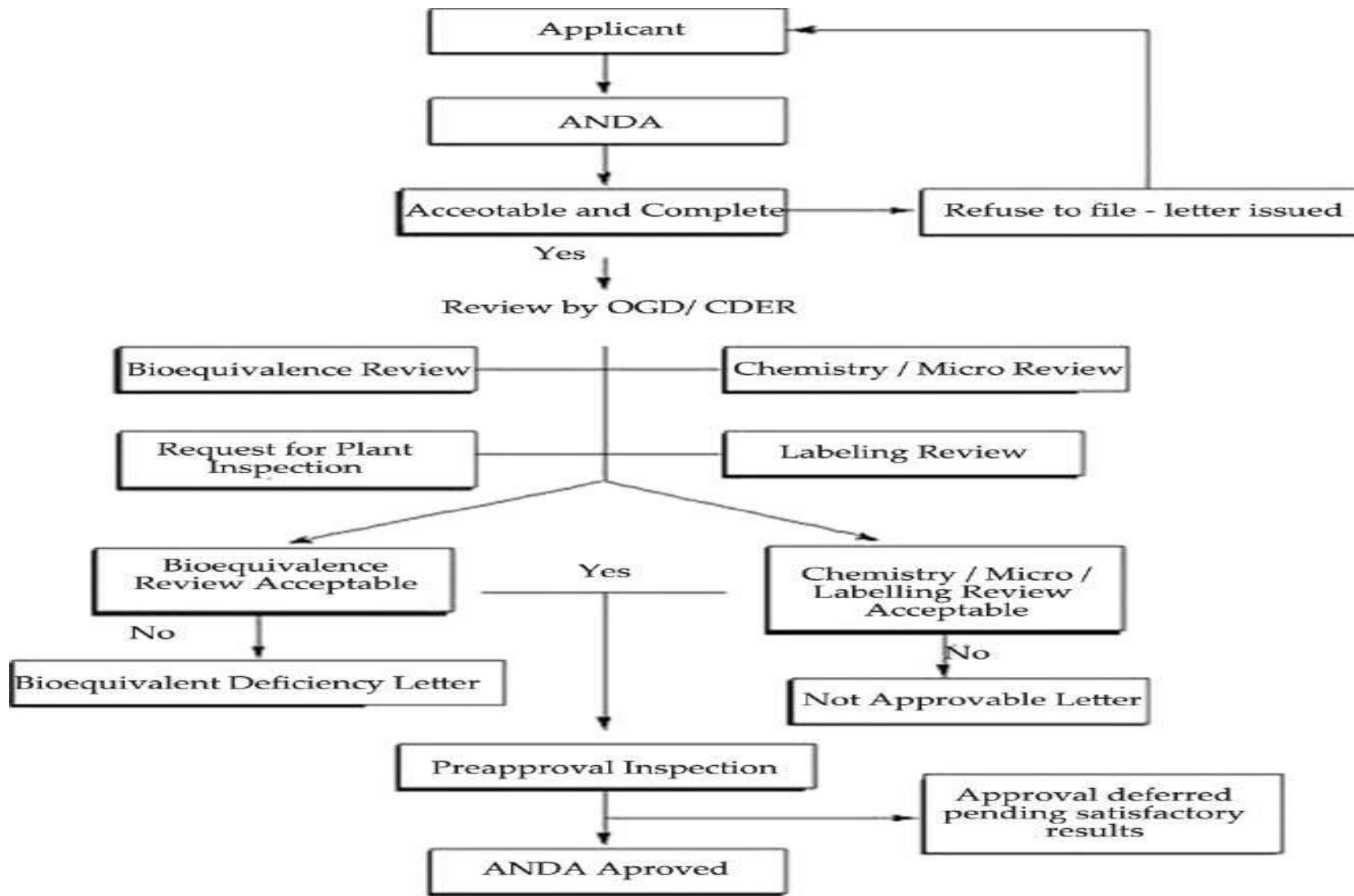


IND - Investigational New Drug  
 NDA - New Drug Application

- 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** 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.

## NDA Chart





## Difference between NDA & ANDA

NDA	ANDA
Applicable for new drug	Applicable for generic drug
Money requirement is high	Less money compare to NDA
12 to 15 year required	1 to 2 year required
Cost of drug is high	Cost of drug is less
Non clinical and clinical study are essential.	Bioavailability and bioequivalence study essential

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## **NDA Requirements**

1. Labelling
2. Pharmacology/Toxicology
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Animal Studies
10. Clinical Studies
11. Bioavailability



## **ANDA Requirements**

1. Labelling
2. Pharmacology/Toxicology
3. Chemistry
4. Manufacturing
5. Controls
6. Microbiology
7. Inspection
8. Testing
9. Bioequivalence

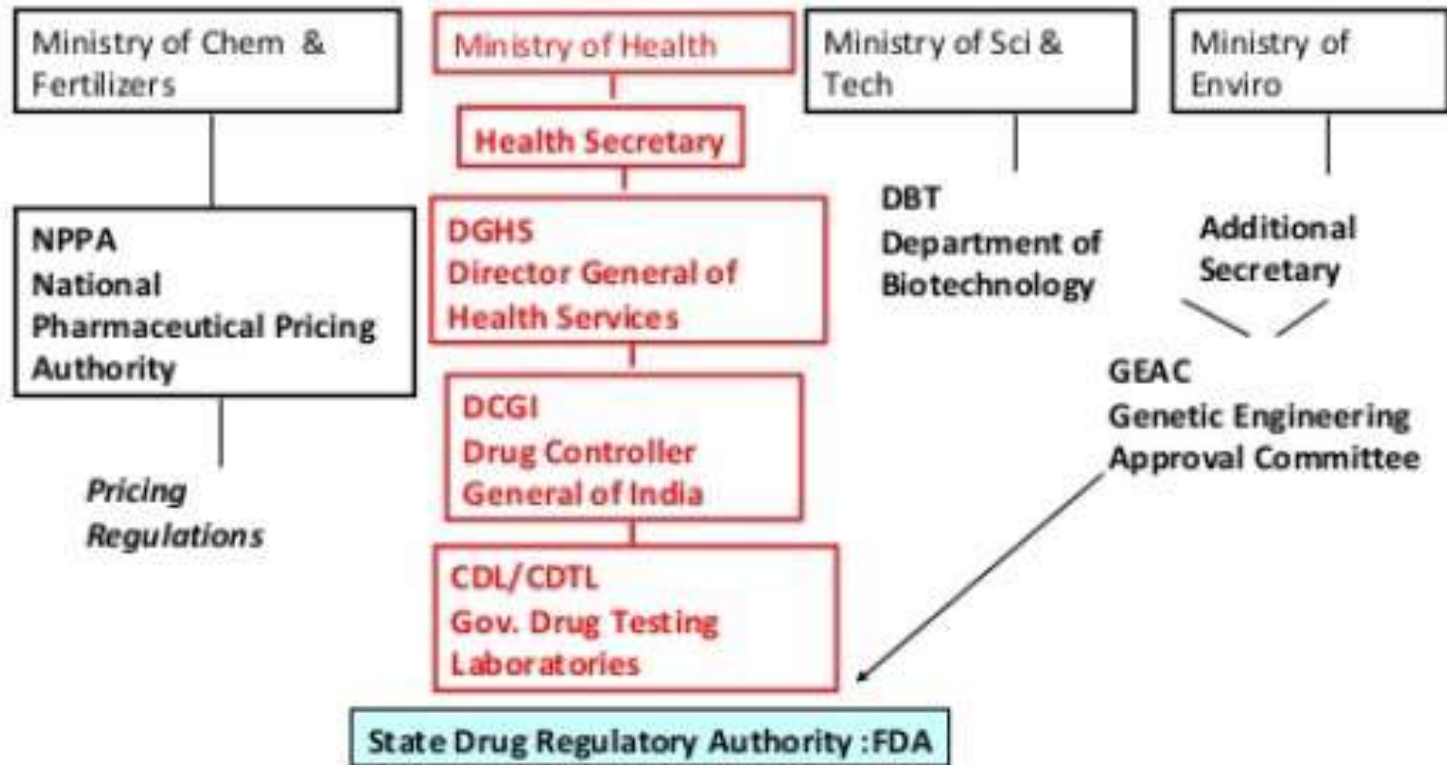
# DRUG APPROVAL PROCESS IN INDIA

- The regulatory scenario in India is changing very fast and DCGI is coming up with precise guideline on each topic. The documentation for product registration in India has become at par with US FDA and seems to objective of DCGI so that data generated in India is acceptable globally.

# HISTORY OF DRUG REGULATION IN INDIA

- Back to British rule when the majority of drugs were imported.
- The Indian Council of Medical Research (ICMR) was created in 1949 to guide and manage medical research.
- The first Drugs and Cosmetics Act came into effect in 1940 and was later amended as the Drugs and Cosmetics Rules of 1945. The 1945 amendment established the CDSCO and the DCGI.
- A specific sub-Drugs and Cosmetics Act was developed, called Schedule Y, to regulate clinical research conduct.
- The Department of Biotechnology was created in 1986 to facilitate various aspects of biotechnology.
- ICMR issued the Ethical Guidelines for Biomedical Research on Human Subjects in 2000, and the CDSCO released the Indian Good Clinical Practice Guidelines in 2001. Together, these agencies assist the licensing authority in issuing final marketing approvals for products.

# REGULATORY AUTHORITIES

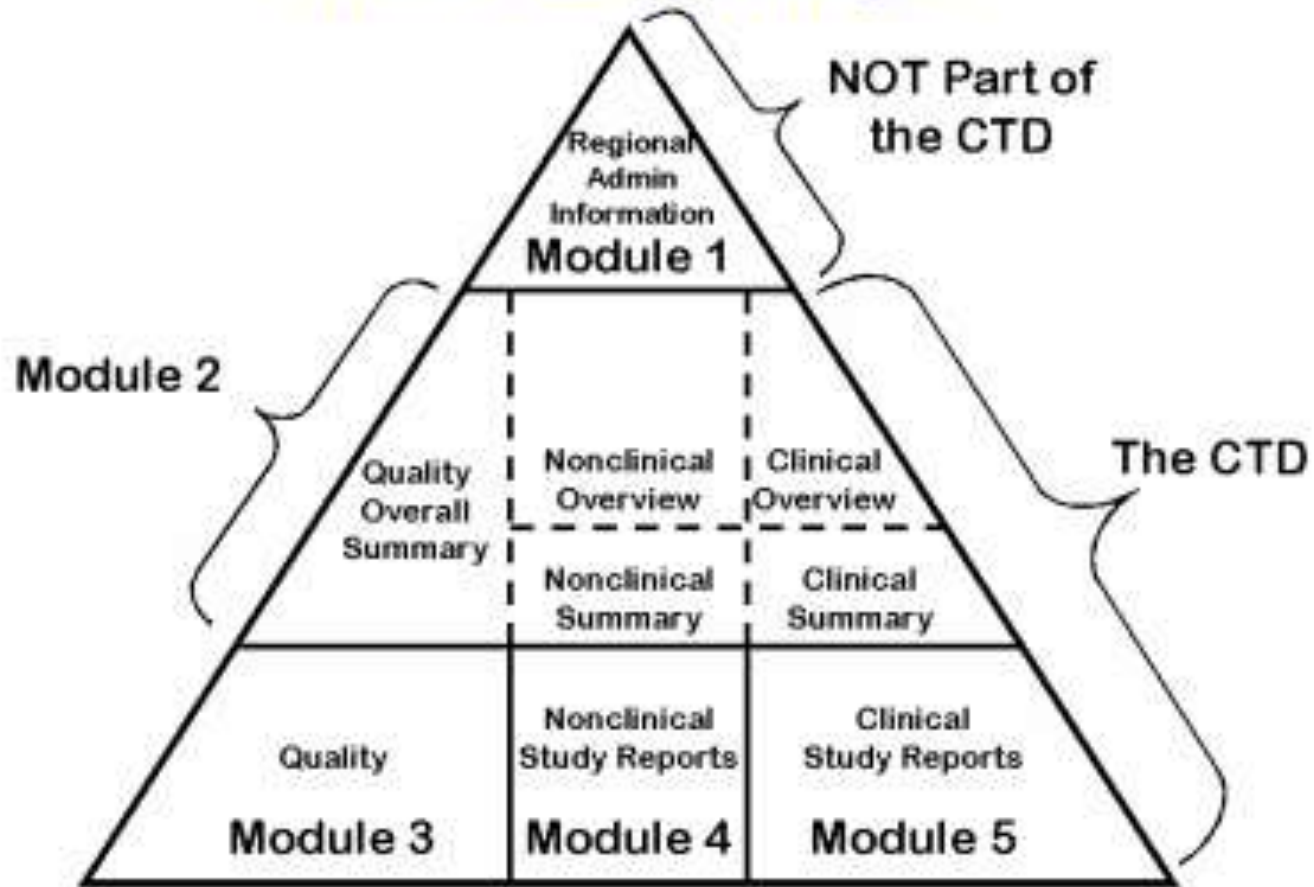


**Table. New Drug Application Forms and Rules<sup>11</sup>**

<b>Form No. and Rules</b>	<b>Purpose</b>
Form 44	Application for permission to import or manufacture a new drug or to begin a new clinical trial
122-A	Application for permission to import a new drug
122-B	Approval for approval to import a new drug
122-D	Permission to import or manufacture fixed dose combination
122-DA	Application for permission to conduct a clinical trial for new drug or investigational new drug
122-DAA	Definition of clinical trial
122-DB	Suspension or cancellation of permission or approval

- At the central level, **DCGI**, under the **Ministry of Health and Family Welfare**, approves the drug or medical device for marketing. Manufacturing licenses are approved at the state level by state drug control authorities. Monitoring is also performed by state agencies in coordination with the CDSCO.
- Manufacturing, importing, or conducting a clinical trial requires permission from the licensing authority through a Form 44 application. The application follows international submission requirements of a **Common Technical Document (CTD)** and has five modules.

# The CTD Triangle



- Form 44 requires information as described in Schedule Y of the Drugs and Cosmetics Act.
- The clinical trial must be conducted in accordance with ethical principles.
- The Act has a special provision (Rule 122-A) to accept international trial data or other information, to allow import, and to waive the clinical trial requirement in the interest of public health. A clinical trial may also be waived for drugs that are approved and have been used in other countries for many years.

# SCHEDULE Y

- Requirements and guidelines to import and/or manufacture of new drug for sale or to undertake clinical trials
- It has outlined extensive study criteria in line with the globally accepted formats such as ICH and US FDA guidelines
- It can be referred to rules 122A, 122B, 122D, 122DA, 122DAA and 122E.

# PURPOSE OF SCHEDULE Y

- To frame guidelines to conduct clinical research
- Control and regulation for new drugs.
- CDSCO formulated GCP under schedule Y in 2005

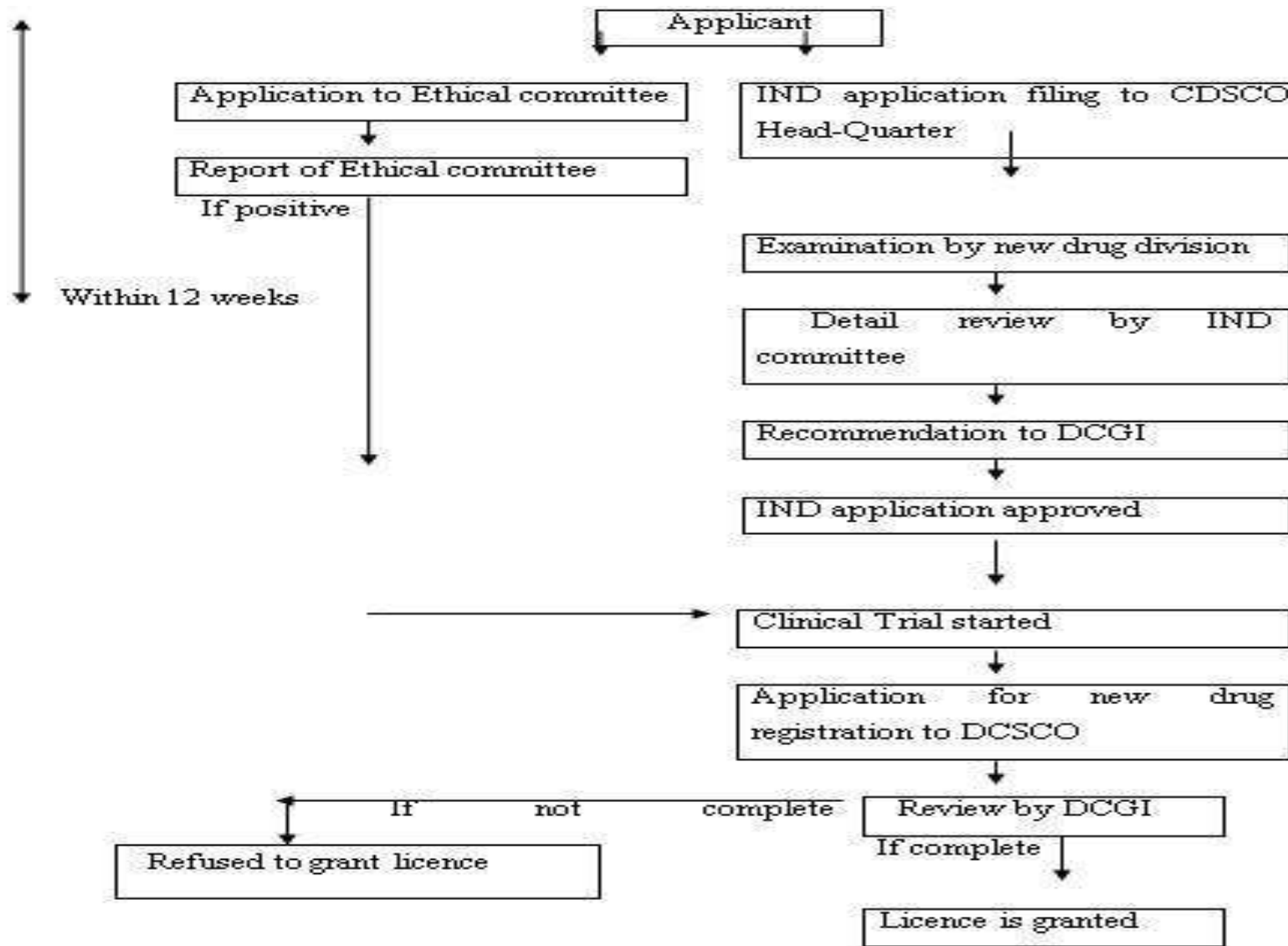


Fig: Flowchart of regulatory requirements for New Drug Application(NDA) in India



**FORM-44**  
[Rules 122A, 122B, 122D and 122DA]

**Application for grant of permission to import or manufacture a New Drug or to undertake clinical trial.**  
**Form 44**

I/We of M/S 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:	
(i) Name of the drug:	
(ii) Dosage Form:	
(iii) Test specification:	
(a) Active ingredients:	
(b) Inactive ingredients:	
(iv) Pharmacological classification of the drug:	
(v) Indications for which proposed to be used:	
(vi) Manufacturer of the raw material (bulk drug substances)	
2. Data submitted along with the application (as per Schedule Y with indexing and page Nos.)	
A. Permission to market a new drug :	
(i) Chemical and Pharmaceutical information	
(ii) Animal Pharmacology	
(iii) Animal Toxicology	

(iv) Human/Clinical Pharmacology (Phase I)	
(v) Exploratory Clinical Trials (Phase II)	
(vi) Confirmatory Clinical Trials (Phase III) (including published review articles)	
(vii) Bio-availability, dissolution and stability study Data	
(viii) Regulatory status in other countries	
(ix) Marketing information:	
(a) Proposed product monograph	
(b) Drafts of labels and cartons	
(x) Application for test licence	
B. Subsequent approval/permission for manufacture of already approved new drug:	
(a) Formulation	
(i) Bio-availability/bio- equivalence protocol	
(ii) Name of the investigator/center	
(iii) Source of raw material (bulk drug substances) and stability study data.	
(b) Raw material (bulk drug substances)	
(i) Manufacturing method	
(ii) Quality control parameters and/or analytical specification, stability report	
(iii) Animal toxicity data	
(c) Approval/Permission for fixed dose combination:	
(i) Therapeutic Justification (authentic literature in [peer-reviewed journals]/text books)	
(ii) Data on pharmacokinetics/pharmacodynamics combination	
(iii) 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:	
(i) Number and date of Approval/permission already granted.	
(ii) Therapeutic Justification for new claim/modified dosage form.	
(iii) Data generated on safety, efficacy and quality parameters.	
Date : 01-01-1970	Signature :

# PRINCIPLE DIFFERENCES BETWEEN US AND INDIA

requirements	US	India
Agency	USFDA	DCGI
Application	ANDA/NDA	MAA
Debarment	yes	no
Approval Time	≈18 months	≈12-18 months
fees	Under \$2 millions- NDA \$51,520-ANDA Application	50,000 INR

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