Dosage Form Design

Lecture 1

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Topics covered through the course

- New drug development and approval process
- Current good manufacturing practices
- Dosage form design pharmaceutical and formulation consideration
- Dosage form design Biopharmaceutical and pharmacokinetic consideration

New drug development and approval process Chapter Objectives

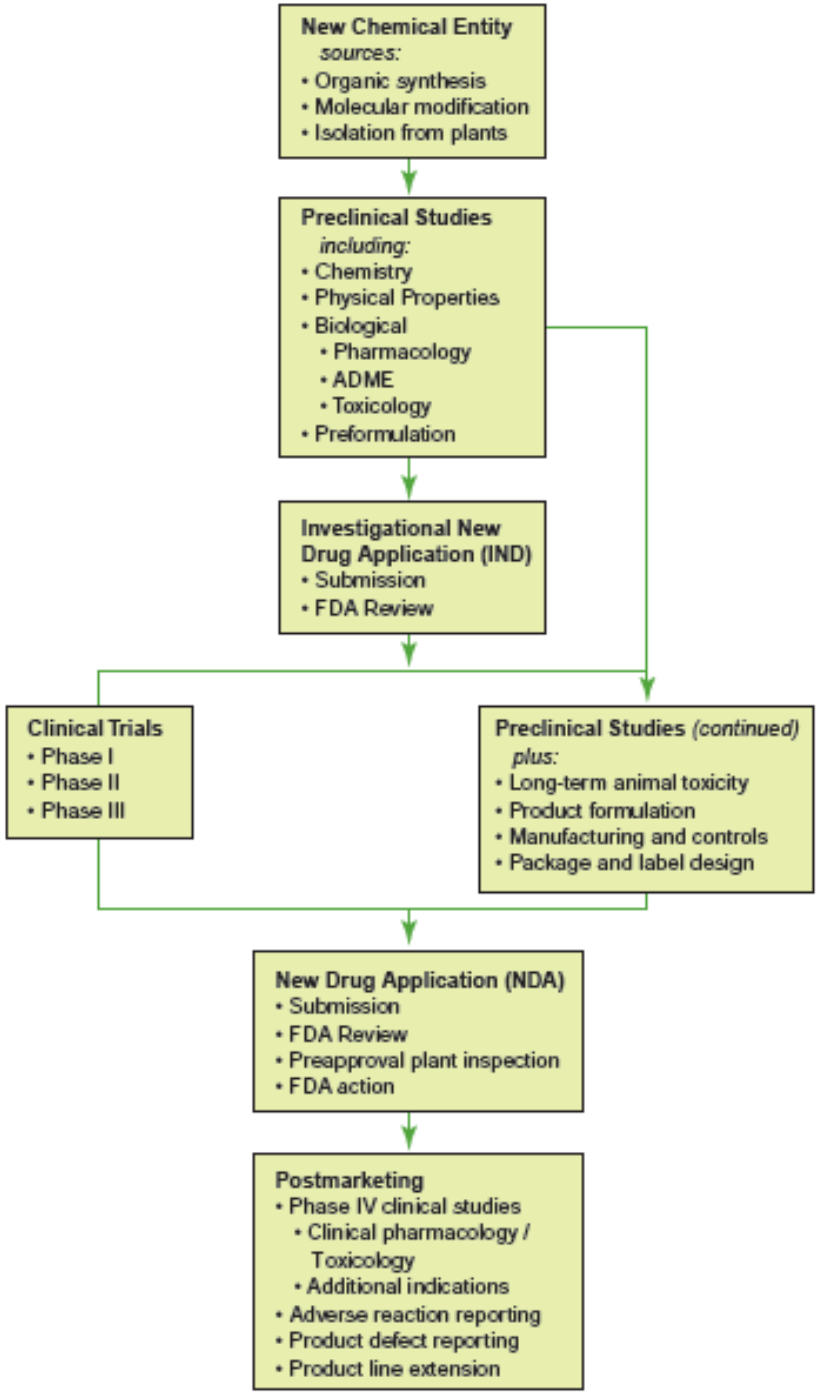
1. Compare and contrast an Investigational New Drug (IND) Application from a New Drug Application (NDA)
2. Differentiate between Phase 1, Phase 2, Phase 3, and Phase 4 clinical trials.
3. Give examples of the sources of new drugs
4. Differentiate between the various methods of drug discovery
5. Delineate the circumstances whereby an old drug could be classified as “new”
6. Define pharmacology, drug metabolism, and toxicology
7. Explain a treatment IND
8. Define an orphan drug
9. Define a package insert and the information contained therein

New Drug Development and Approval Process

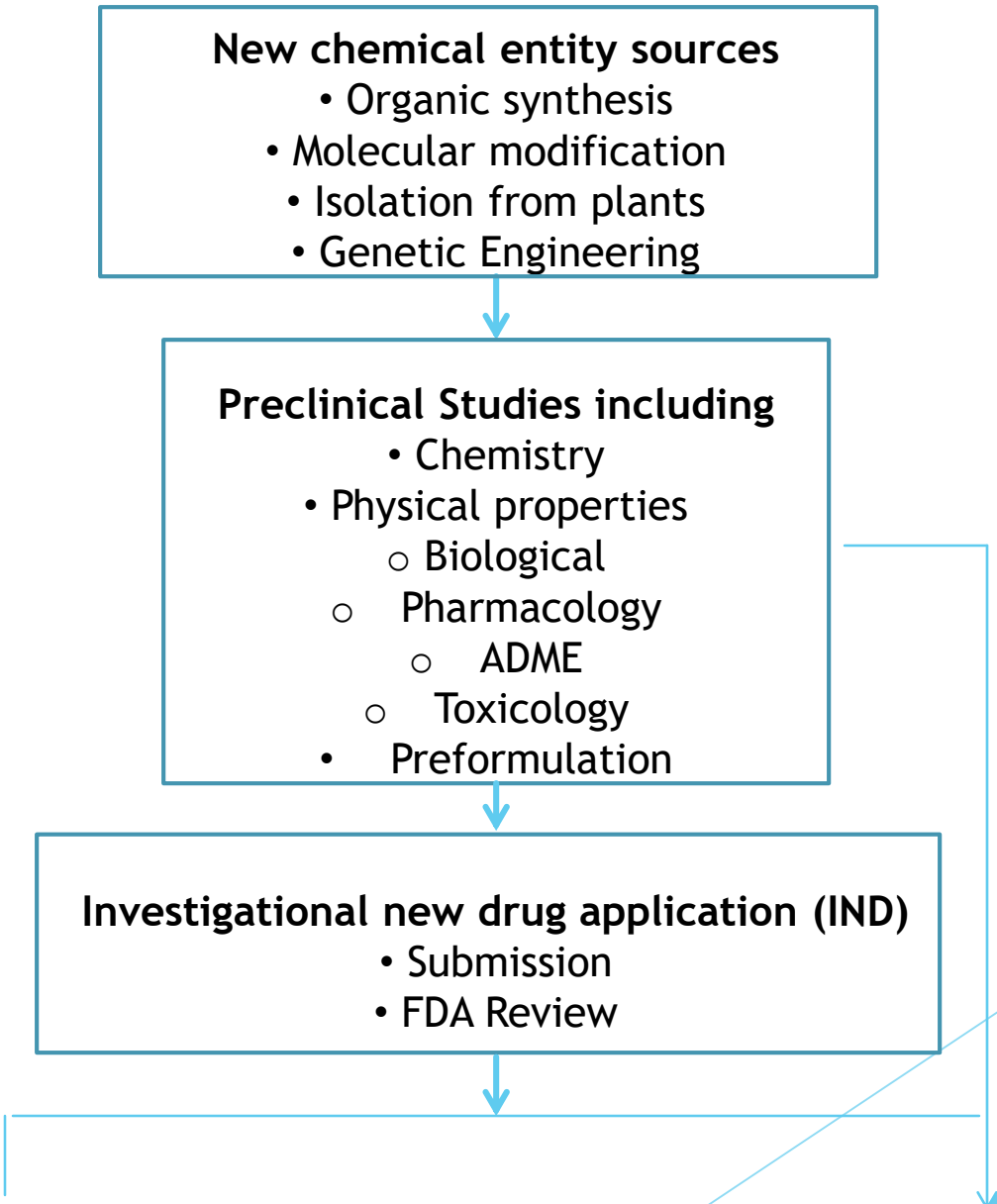
- To gain approval for marketing, a drug's sponsor (e.g., a pharmaceutical company) must demonstrate, through supporting scientific evidence, that

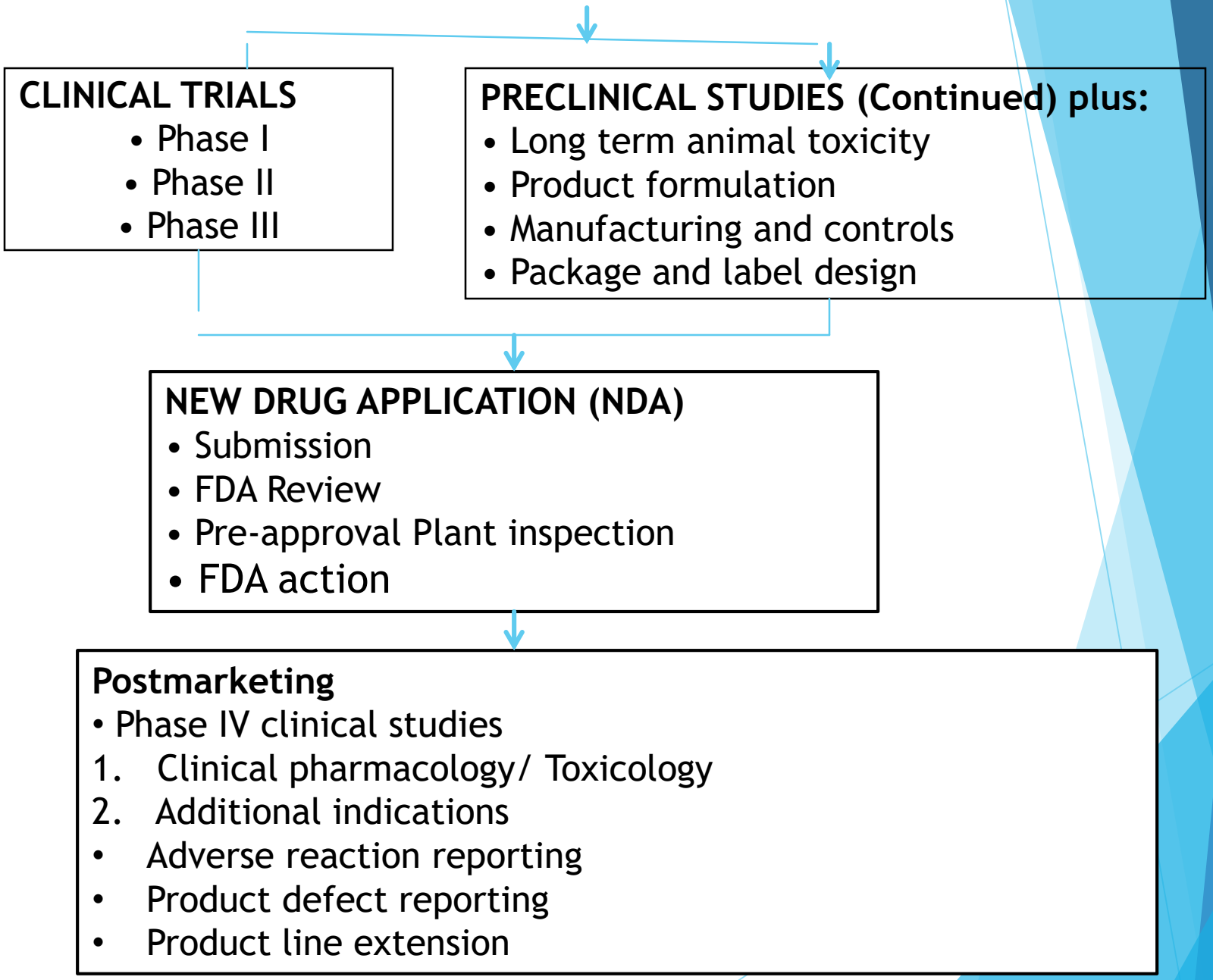
1. The new drug or drug product is safe and effective for its proposed use.
2. The various processes and controls used in producing the drug substance and in manufacturing, packaging, and labeling are properly controlled and validated to ensure that the product meets the established standards of quality.

- The process and time course from drug discovery to approval for marketing can be lengthy and tedious


New Chemical Entity
sources:
• Organic synthesis
• Molecular modification
• Isolation from plants
Preclinical Studies
including:
• Chemistry
• Physical Properties
• Biological
• Pharmacology
• ADME
• Toxicology
• Preformulation
Investigational New Drug Application (IND)
• Submission
• FDA Review
Clinical Trials
• Phase I
• Phase II
• Phase III
Preclinical Studies (continued)
plus:
• Long-term animal toxicity
• Product formulation
• Manufacturing and controls
• Package and label design
New Drug Application (NDA)
• Submission
• FDA Review
• Preapproval plant inspection
• FDA action
Postmarketing
• Phase IV clinical studies
• Clinical pharmacology / Toxicology
• Additional indications
• Adverse reaction reporting
• Product defect reporting
• Product line extension

A schematic representation of the process for new drug development




CLINICAL TRIALS
• Phase I
• Phase II
• Phase III
PRECLINICAL STUDIES (Continued) plus:
• Long term animal toxicity
• Product formulation
• Manufacturing and controls
• Package and label design
NEW DRUG APPLICATION (NDA)
• Submission
• FDA Review
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Postmarketing
• Phase IV clinical studies
1. Clinical pharmacology/ Toxicology
2. Additional indications
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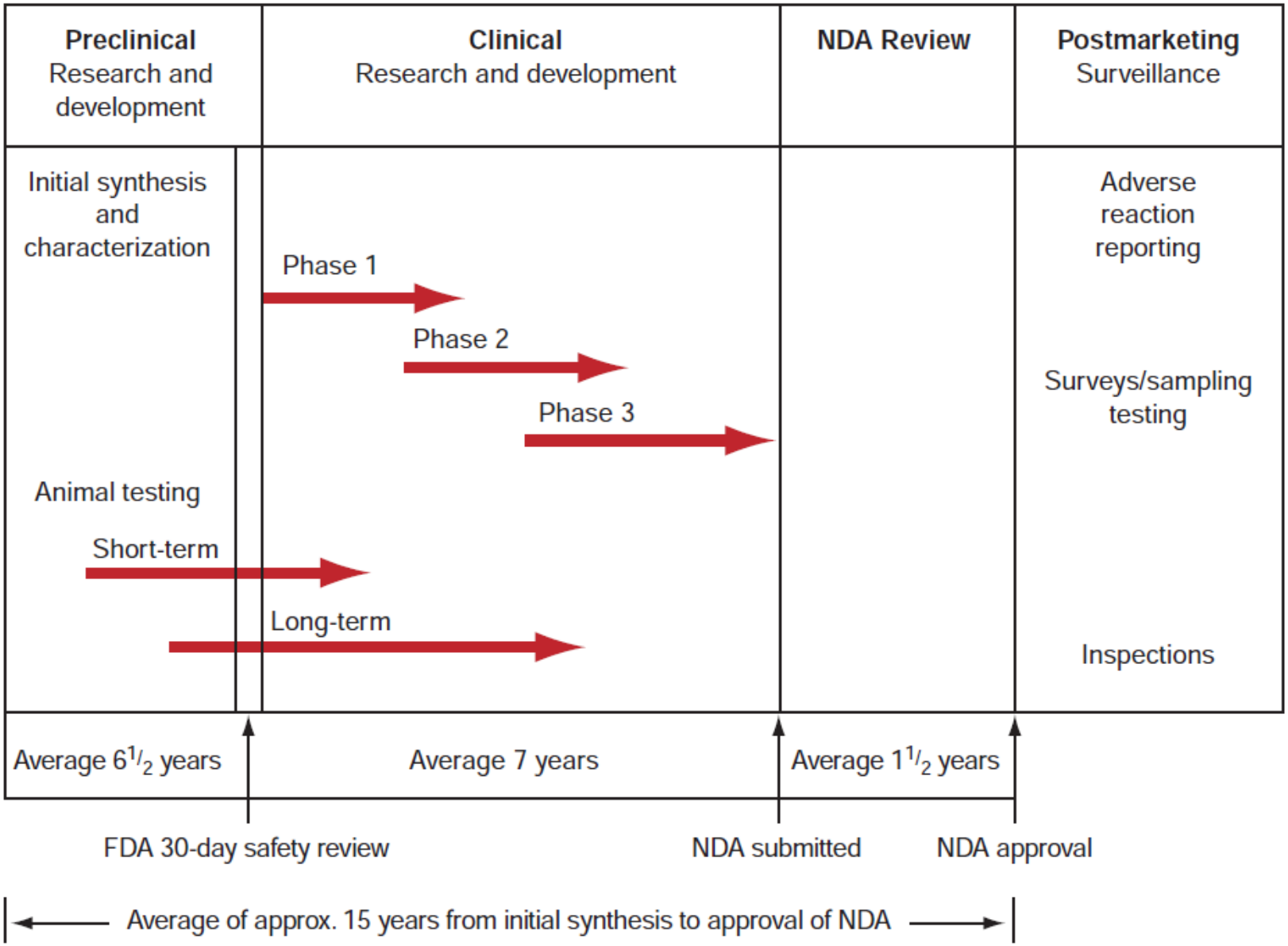

Time course for the development of a new drug

What will happen after the discovery (e.g., synthesis) of a proposed new drug agent ???

- Preclinical studies
- File an IND (Investigational New **Drug)** application with the FDA for initial testing in humans clinical trials. Phase 1, Phases 2 and 3
- Laboratory work continues
- At the completion of the carefully designed preclinical and clinical studies, the drug's sponsor may file an NDA (new drug application) seeking approval to market the new product.
- **The FDA approval of a NDA indicates that the body of scientific evidence submitted sufficiently demonstrates that the drug or the drug product is safe and effective for the proposed clinical indication, that there is adequate assurance of its proper manufacture and control, and that the final labelling accurately presents the necessary information for its proper use.**

Some products, however, have been approved and later removed from the market for safety reasons, including the following:

Astemizole (Hismanal) / Hismanal could cause fatal heart rhythm disturbances in high doses or in combination with other drugs

Cerivastatin (Baycol)/ In August 2001, the FDA pulled the cholesterol-lowering drug Baycol off the market. The drug appeared to be responsible for 31 deaths due to kidney failure.

Troglitazone (Rezulin)/ an antidiabetic and anti-inflammatory drug, Glaxo removed troglitazone from the market in Britain on December 1, 1997. ... He estimated that the drug could be linked to over 430 liver failures

The content of a product's approved labeling represented by **the package insert**

- In addition to the general new drug approval process, special regulations apply for the approval of certain new drugs to treat serious or life-threatening illnesses, such as AIDS and cancer. These may be placed on an accelerated of fast-track program for approval. Also if there is no satisfactory approved drugs for serious medical condition, special protocol may be issued permitting the use of IND before approval by NDA. This type of protocol is called Treatment IND.
- Treatment INDs often sought for orphan drugs, which are targeted for small numbers of patients who have rare conditions or diseases for which there are no satisfactory alternative treatments.
- Under the Orphan Drug Act of 1983 as amended, an **orphan disease is defined as a rare disease or condition that affects fewer than 200,000 people in the United States.**

Treatment IND

- The objective is to make promising new drugs available to desperately ill patients as early as possible in the drug development
- For products to be considered for a treatment IND, the drug must be under active process. investigation in a controlled clinical trial with sufficient evidence of its safety and efficacy demonstrated to support its use in the intended patients
- There are four requirements that must be met before a treatment IND can be issued:

1) the drug is intended to treat a serious or immediately life-threatening disease;
2) there is no satisfactory alternative treatment available;
3) the drug is already under investigation, or trials have been completed;
4) the trial sponsor is actively pursuing marketing approval.

SNDA

- A sponsor of an approved NDA may make changes such as labelling or formulation.
- Depending on the changes proposed, some require FDA approval before implementing; others do not.
- If FDA approval is required then the manufacturer is required to submit for approval a **supplemental new drug application (SNDA).**

Among the changes requiring prior approval are:

1. A change in the method of synthesis of the drug substance
2. Use of a different facility to manufacture the drug substance where the facility has not been approved through inspection for Current Good Manufacturing Practice standards within the previous 2 years
3. Change in the formulation, analytical standards, method of manufacture, new dosage form, new strength of a drug or in-process controls of the drug product
4. Use of a different facility or contractor to manufacture, process, or package the drug product
5. Change in the container and closure system for a drug product
6. Extension of the expiration date for a drug product based on new stability data
7. Any labeling change that does not add to or strengthen a previously approved label statement

Changes that does not require prior approval by FDA

1. Any labeling change that add to or strengthen a previously approved label statement
2. any analytical changes made to comply with USP/NF
3. Extension of the expiration date based on full shelf life data obtained from a protocol in the approved application
4. Change in the size (not the type of system) of the container used for solid dosage forms

ANDA

- Abbreviated new drug application (ANDA) is application for generic drugs previously approved by NDA in which non-clinical laboratory studies and clinical investigation could be omitted **except for those pertaining to the drug bioavailability.**
- These applications are usually filed for duplicates (generic copies) of drug products previously approved under a full NDA and for which the FDA has determined that information on the exempted nonclinical and clinical studies is already available at the agency
- Generic drug applications are called **"abbreviated"** because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, a generic applicant must scientifically demonstrate that its product is bioequivalent (i.e., performs in the same manner as the innovator drug).
- A generic drug product is one that is comparable to an innovator drug product in dosage form, strength, route of administration, quality, performance characteristics, and intended use.

Reference

Ansel's pharmaceutical dosage forms and drug delivery systems , tenth edition