New Drugs: Their Development & Evaluation

New Drug Development

- Idea or hypothesis
- Design & synthesis of substances
- Studies on tissues & animal **(preclinical studies)**
- Studies on man **(clinical studies)**
- Official license (registration & market authorization)
- Post-marketing studies

Aims of Therapeutic Evaluation

- To assess **efficacy, safety & quality** of new drugs
- To **expand indications** for the use of current drugs
- To **protect public health**

Drug Development

- **Drugs** are **chemical substances** useful in **prevention & diagnosis & treatment** of diseases
- **The process of drug development may be abandoned at any stage** including **after marketing (safety, inadequate efficacy)**

Drug Development

- New drug development is **enormously expensive**
- **Cost of development of a new chemical entity from synthesis to market US $ 500 million**
- **The process may take 10-15 years**

Origin of Drugs

- **Natural sources:**
  - **Plant** origin like **morphine**, **digoxin**, **atropine**
  - **Micoorganisms** as fungi & bacteria synthesizing **antibiotics**
  - **Animal** origin like **hormones (insulin), heparin**
  - **Mineral** origin like **iron, calcium**

Origin of Drugs

- **Synthetic** when **synthesized chemically in laboratories**
- **These represent majority of drugs**, as they are easily manufactured & cheaper like **aspirin, paracetamol & propranolol**

Medicines

- **Medicines are drugs formulated in a suitable way for administration & use by patients**
- **Medicines** consist of the **active drug** combined with **excipients** that give it **shape, size, stability** & other criteria as **starch**, **Arabic gum** & many other substances

Therapeutic Investigation

- There are **three questions** to be answered during drug development:
  1. **Does the drug work?**
  2. **Is it safe?**
  3. **What is the dose?**

Phases of Drug Development

1. Pre-clinical studies in animals
2. Clinical studies in human

1. Pre-clinical studies in animals including:

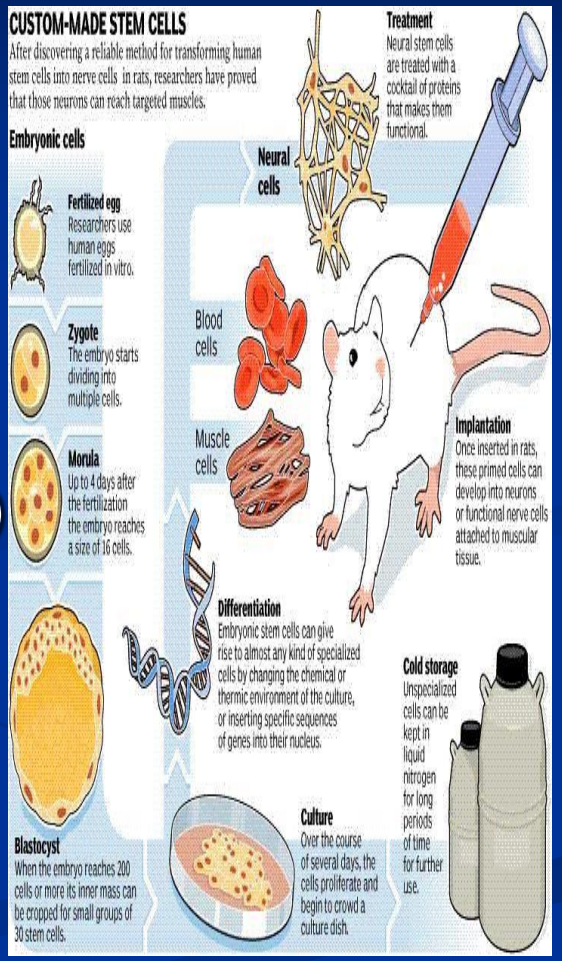
A. General pharmacology studies:

- Pharmacokinetic studies
- Pharmacodynamic studies
- Dose, preparation & routes of administration

1. Pre-clinical Studies in Animals including:

B. Toxicological studies

- **Acute toxicity**
- **Special toxicity studies:**
  - **Reproductive system**
  - **Mutagenesis** (mutation production)
  - **Oncogenesis** (malignancy)
  - **Teratogenicity** (harmful effects on foetus)



2. Clinical Studies in Human

- These are carried out **in humans** in **clinical trials centers** **&** **in hospitals** under supervision of qualified investigators
- **These include:**

2. Clinical studies in human

- Phase 1 studies
- Phase 2 studies
- Phase 3 studies
- Phase 4 studies

Phase 1 Studies (Human pharmacology)

- These are performed on **a limited number of healthy volunteers (20-50 subjects)**

The aims of these trials are:

- **Study of the general pharmacology of drug**
- **Pharmacokinetics (ADME)**
- **Pharmacodynamics (biological effect)**
- **Tolerability, efficacy & safety (associated adverse effects)**

Phase 2 Studies (Therapeutic exploration)

- These are carried out on **a limited number of patients (50-300)** to:
- **General pharmacology of drug in patients**
- **Pharmacokinetics**
- **Pharmacodynamics**
- **Establish safety of drugs**
- **Assess potential therapeutic effects, comparison with placebo**

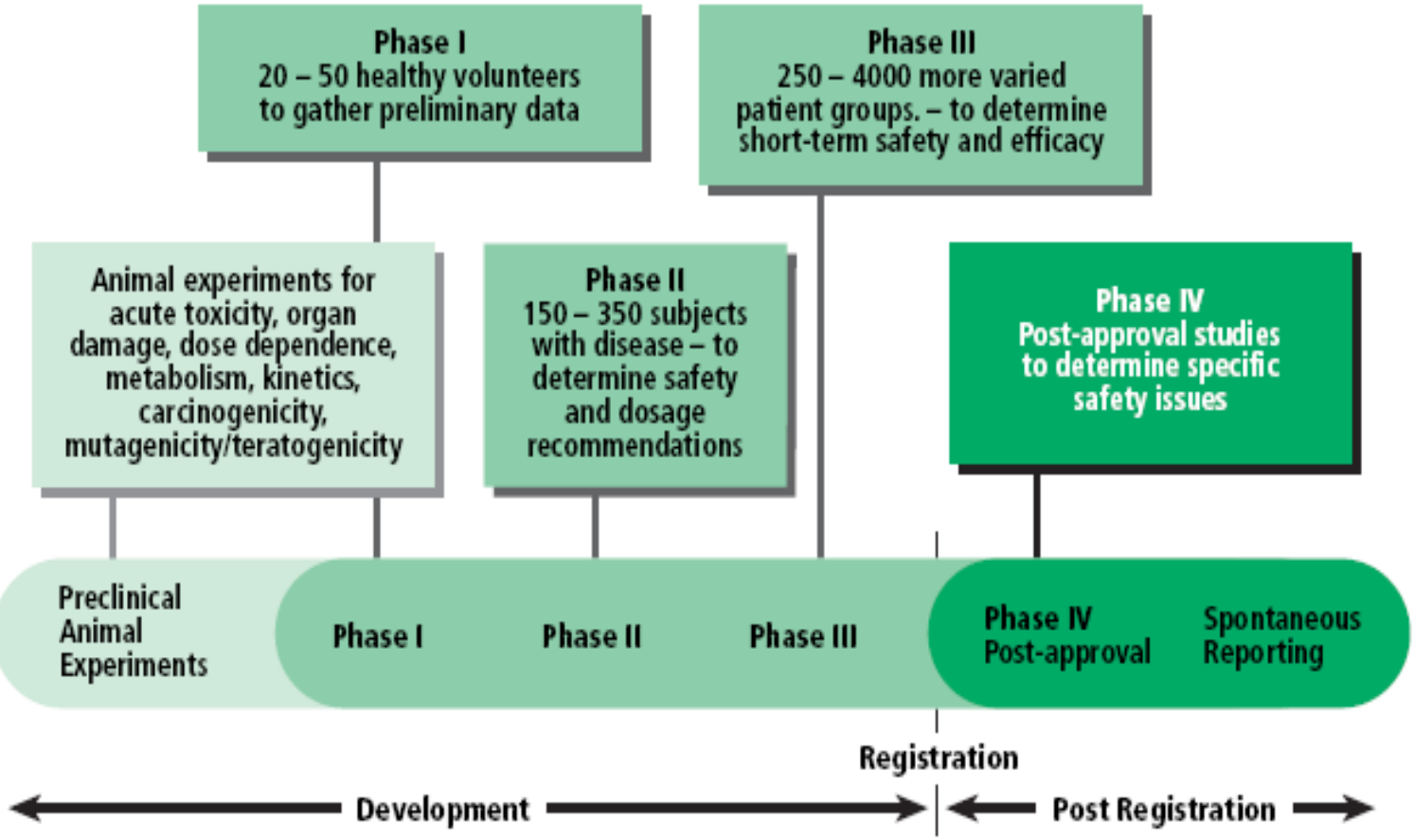
Phase 3 Studies (Therapeutic confirmation)

- **Randomized control trials**
- These include **multi-centre comparative studies** on **a large number of patients (250-1000)** to establish therapeutic efficacy & safety, **comparison with existing drugs**
- **Short term efficacy & safety**

Phase 4 studies (Therapeutic use)

- These include **post-marketing surveillance (post-authorization studies) (2000- 10,000)** to look for possible **long term effects of drugs**
- **Long term efficacy & safety**

Figure 1 Clinical development of medicines



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Clinical Trials

- **Clinical trials** are carefully and ethically designed **controlled experiments** performed on **human beings** to evaluate certain aspects of drug studies

Aims of clinical trials

- Whether treatment is of value
- Magnitude of that value compared with other remedies
- Type of patients in whom it is of value
- Best method of applying treatment (how often, dosage of drug)
- Disadvantages & dangers of treatment

Fundamental to any clinical trial are:

- An hypothesis
- Definition of primary endpoints
- Method of analysis
- A protocol

Other factors when designing a trial:

- Characteristics of patients
- Size of trial
- Duration
- Method of monitoring
- Use of interim analyses

Subjects included in the studies are either:

- Healthy normal volunteers or
- Patients

Patients excluded from clinical trials include:

- Children
- Pregnant women
- Mentally ill patients

Techniques to avoid bias

- **Randomization:**

  - Introducing element of **chance** into **selection & allocation of subjects to treatments**

- **Blinding**

Criteria of clinical trials (CCT)

- **Objective:** should be clear & limited to one aim
- **Careful design:** A protocol should be prepared that shows design of the CCT prepared by clinical pharmacologist, physician & statistician
- **Crossover design:** when **each subject is randomized to a sequence of two or more treatment**, and **he acts as his own control for treatment comparisons**

Criteria of clinical trials

- Clinical trials may be of **non-crossover design** recruiting **different subjects as a control group**
- **Balanced** regarding **sex**, **age**, weight & disease state
- **Double-blind technique** when **neither investigator nor subject knows about treatments they are receiving.** This technique is important to:
  - **Eliminate investigator bias**
  - **Eliminate** patients or **subject** bias
  - Allow the use of **placebo**

- **Single-blind** technique is described **when investigator knows but patient does not know treatment given to him**
- **Control group** is used who will receive either **placebo or a standard therapy**
- **Statistical analysis** should be planned initially including the proper tests used

The use of placebo

- It is a **pharmacologically inert** substance **identical** in all aspects to the active treatment indistinguishable from it

It is intended to:

- **Eliminate** observer or investigator **bias**
- Detect **non-pharmacological effects** of drugs **(placebo effects)**
- A **control** for statistical comparison

Conditions that do not require use of placebo

- **Therapeutic studies** as it is **unethical to deprive patients of treatments. A standard therapy is chosen instead of placebo**
- **When the active compound can be identified**

  e.g. a vasodilator, alkaptonuria (nitisinone)
- **Dose-finding studies**
- **Pharmacokinetic studies**

Ethical Considerations in Clinical Trials

- **Declaration of Helsinki**
- The declaration of Helsinki (1964, 1975) sought to **clarify the ethical principles governing clinical research involving human subjects** emphasizing **informed consent & proper scientific research design. It is the mission of doctor to safeguard health of people.** The doctor's knowledge & conscience are dedicated to the fulfillment of this mission

Recommendations are essential as a guide to doctors in clinical research:

- **Risks & benefits** must be carefully **assessed**
- **Nature, purpose & possible hazards must be explained to subjects by doctor**

Recommendations are essential as a guide to doctors in clinical research:

- **Informed written consent** must be obtained
- **Subjects must be free to withdraw** from clinical trial anytime
- The investigators should discontinue research, if in their judgment it may if continued be harmful to subjects

ClinicalTrials.gov

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- www.ClinicalTrials.gov