

New Drugs: Their Development & Evaluation



Dr. Mohammed Al-sbou
Professor in Clinical Pharmacology
Faculty of Medicine, Mutah University

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:

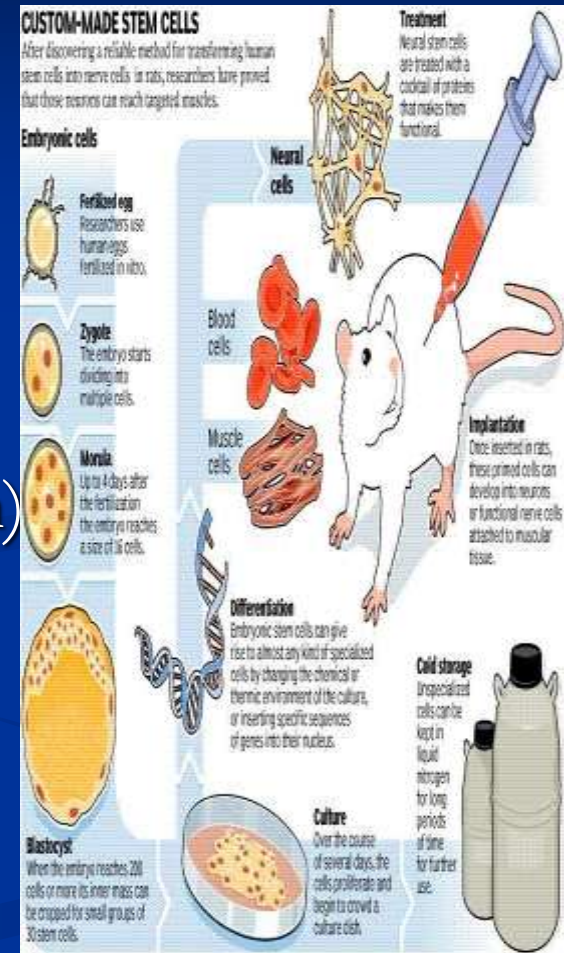
- ❑ Pharmacokinetic studies
- ❑ Pharmacodynamic studies
- ❑ Dose, preparation & routes of administration



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

Phases of Drug Development

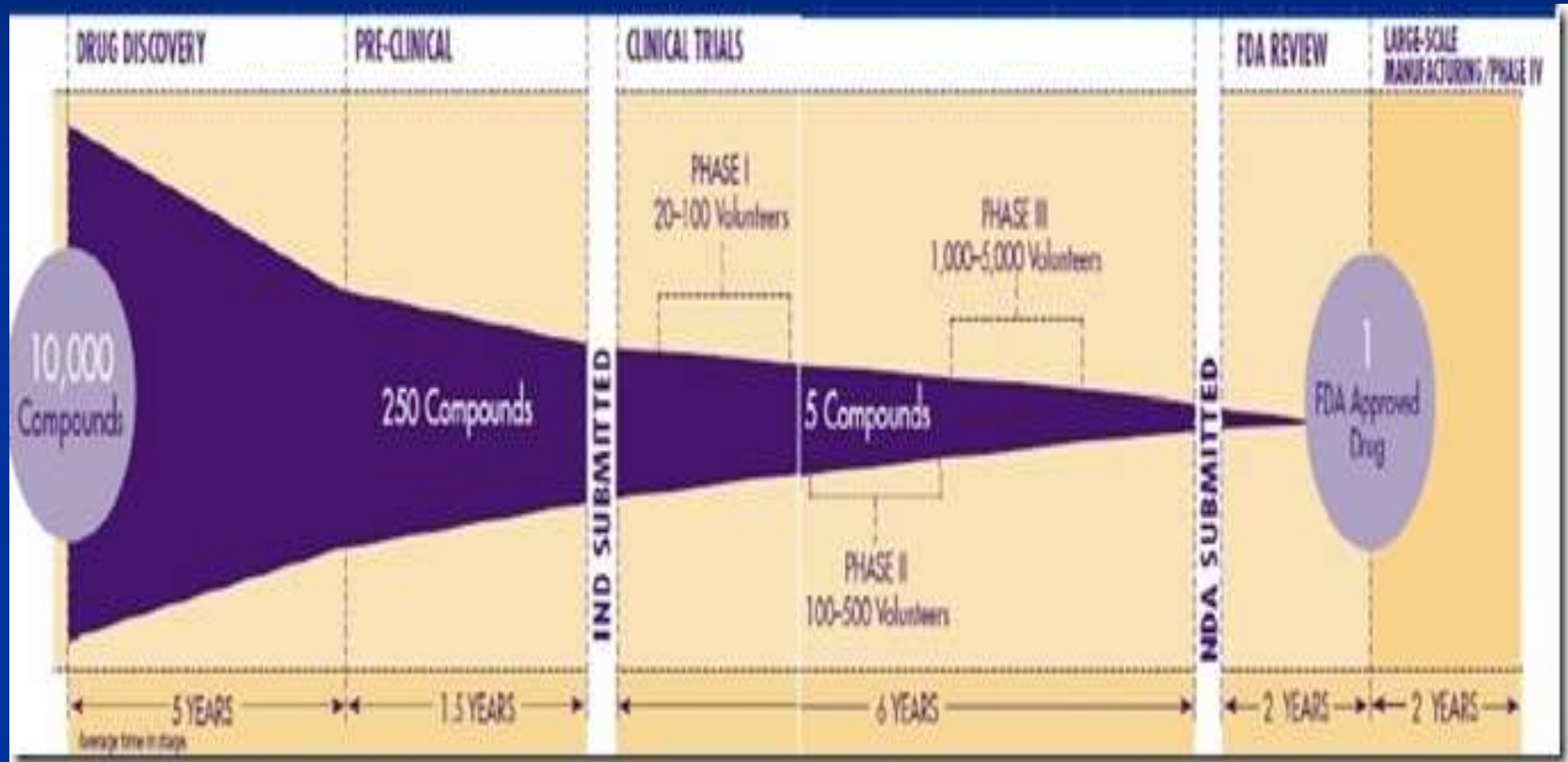
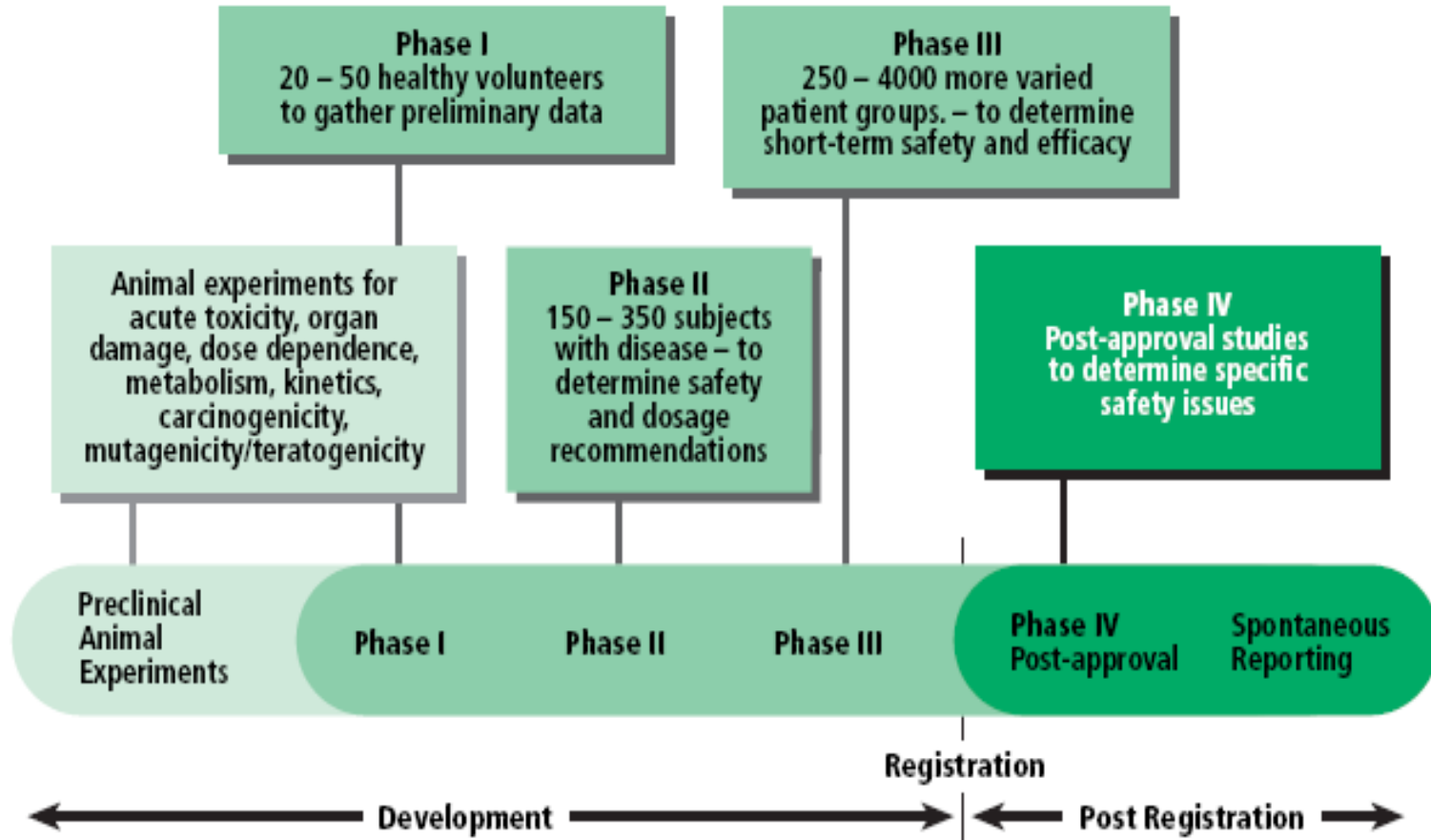


Figure 1 Clinical development of medicines



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

DevelopAKUre

- ▶ **4 years international multicenter clinical trials**, funded by European commission (FP7) - **€ 6 million**
- ▶ 12 European partners & **Jordan** (Faculty of medicine-mutah university)
- ▶ 3 trial sites: **UK (Liverpool), France (Paris) & Slovakia (Piestany)**
- ▶ **Aims:** to study the potential effectiveness & safety of nitisinone in treating alkaptonuria (AKU)



SONIA 2 (Suitability of Nitisinone in AKU)

- **140 patients**
- Patients were from Spain, France, Belgium, Italy, Netherlands, Germany, Slovakia & **Jordan**
- **19 Jordanian patients**
National Institute for Rheumatic diseases, Slovakia



Procedures

Bloods:

- HGA, tyrosine, nitrotyrosine
- Bone/muscle/cartilage markers
- Biochemistry profiles, metabolomics
- Genetics
- Acute phase reactants, cytokines

Urine:

- HGA, tyrosine, nitrotyrosine
- Bone & cartilage markers
- Metabolomics

Yearly:

- Abdominal ultrasound, Audiometry
- ECG, Echocardiogram
- Bone density scan (Dexa)
- Isotope scintigraphic scan
- Medical Photographs

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